EXHIBIT H

Declaration of Bruce P. Lanphear, M.D., M.P.H.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

CONCERNED PASTORS FOR SOCIAL ACTION, et al.,

Plaintiffs,

v.

NICK A. KHOURI, et al.,

Defendants.
_____/

Case No. 16-10277

Hon. Mark A. Goldsmith

Mag. J. Stephanie Dawkins Davis

DECLARATION OF BRUCE P. LANPHEAR, M.D., M.P.H.

I, Bruce Lanphear, do hereby affirm and state:

Introduction and Qualifications

1. I am a medical doctor. I received my M.D. in 1986 from the University of Missouri at Kansas City. I completed an internship at the University of Arkansas for Medical Sciences (1986-87), and a fellowship in general academic pediatric research at the University of Rochester School of Medicine (1992-95). Since 1989, I have been certified by the American Board of Medical Specialties, with a specialization in general preventative medicine and public health.

2. I also received a Masters in Public Health from the Tulane School of Public Health and Tropical Medicine in 1988.

3. I am presently a Clinician Scientist at the Child and Family Research Institute at British Columbia's Children's Hospital and a Professor on the Faculty of Health Sciences at Simon Fraser University.

4. My research focuses on quantifying and preventing health effects in children that result from exposures to environmental toxins such as lead.

5. Since completing my academic training, I have served as a member of numerous public health agencies and task forces including the Science Advisory Board for Evaluating the Hazards of Partial Water Line Replacement for the U.S. Environmental Protection Agency (EPA) and the Peer-Review Panel for the National Toxicology Program of the U.S. Department of Health and Human

Services Monograph on Health Effects of Low-Level Lead. I was also a member of two National Academies of Science Committees, one on "Ethical Consideration for Research on Housing-Related Health-Hazards involving Children" and the other on "Contaminated Drinking Water at Camp Lejeune." I serve as an editorial board member for several scientific journals, including PLoS Medicine and Environmental Health Perspectives.

6. A more complete description of my educational and work experience, as well as a complete list of my publications, is appended as Exhibit 1 to this declaration.

7. By virtue of my medical and public health training, my clinical work, my research, and my knowledge of pertinent scientific literature, I am often considered by my peers as an expert on lead toxicity and the sources and effects of lead exposure, particularly in children.

8. All of the information set forth in this declaration is based upon my education, personal knowledge, and experience as well as my review of the documents attached as Exhibits 2-11.

Basics of lead exposure through water

9. Lead is a neurotoxin and a pervasive environmental health threat.

10. Lead exposure can occur in many ways. The most common route of exposure for children is ingestion of lead-contaminated dust, soil, or water.

11. Lead exposure from dust and soil is primarily due to the presence of lead-based paint and legacy lead gasoline emissions.

12. Exposure to lead from drinking water is due to the presence of lead-containing water infrastructure, particularly in older homes and cities. Lead is soluble and can enter drinking water through the corrosion of plumbing materials, including lead pipes and fixtures.[1]

13. As lead in paint and gasoline has been banned, lead in water has become a more important source of exposure in some communities.[2]

14. Lead exposure through water can occur by drinking or cooking with contaminated water. Infants may be exposed by ingesting formula prepared with lead-contaminated tap water. Lead can also pass from a mother to a developing fetus and from nursing mothers to their babies through breastmilk.

15. An individual's level of exposure to lead varies based on age and other factors.

16. Infants are especially vulnerable to lead-contaminated water because their primary interaction with their environment is what they drink.[3] For infants

[1] Ronnie Levin et al., *Lead Exposures in U.S. Children, 2008: Implications for Prevention*, 116 Envtl. Health Persp. 1285, 1287 (2008) (attached as Ex. 2).

[2] Patrick Levallois et al., *The Impact of Drinking Water, Indoor Dust and Paint on Blood Lead Levels of Children Aged 1–5 years in Montréal (Québec, Canada)*, 24 J. Exposure Sci. & Envtl. Epidemiology 185, 185 (2014) (attached as Ex. 3).

consuming formula, tap water may account for more than eighty-five percent of their total lead exposure.[4] Infants also absorb lead at higher rates than adults, particularly lead from drinking water. Infants can absorb forty to fifty percent of water-soluble lead they ingest compared with three to ten percent for adults.[5] Young children also have a greater risk of exposure from lead-contaminated water because, pound for pound, they drink more water than older children and adults.

17. Infants and children who have iron or calcium deficiencies also more readily absorb lead. This is because lead mimics iron and calcium in the way it is absorbed in the gastrointestinal tract. The majority of lead is stored in bones; lead in the blood of young children is a reliable indicator of ongoing exposures.

18. The majority of lead absorbed by the body (more than seventy percent) is stored in a person's bones, where it can remain for years. Lead in bones can be released during times of physiological change, including stress, pregnancy,

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[3] Michael W. Shannon & John W. Graef, *Lead Intoxication in Infancy*, 89 Pediatrics 87, 89-90 (1992) (attached as Ex. 4).

[4] Mona Hanna-Attisha et al., *Elevated Blood Lead Levels in Children Associated With the Flint Drinking Water Crisis: A Spatial Analysis of Risk and Public Health Response*, 106 Am. J. Pub. Health 283, 284 (2016) (attached as Ex. 5).

[5] *Id.*

lactation, fractures, and menopause. The concentration of lead in a woman's blood, for instance, increases by about thirty percent after menopause.[6]

19. Testing a person's blood lead level is not the best way to identify an increased risk of lead exposure from drinking water; the best approach is to test their tap water for lead *before* they are exposed. For adults, the half-life of lead in blood is thirty days; for children, it can range from weeks to months. As a result, measuring lead in blood may not fully capture a person's lifetime exposures.

20. Lead poisoning is more likely to affect non-Hispanic black children and children from low-income families.[7] People who live in older homes and rental housing are also at increased risk for higher blood lead concentration, as are people who consume diets low in nutrients and calories. [8]

Health effects of lead exposure

21. Lead damages numerous organ systems and causes permanent, irreversible injuries to children's developing brains. Even at low levels of exposure, lead is harmful to both children and adults. In short, there is no safe level of exposure to lead.

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[6] Health Effects of Low-Level Lead, Nat'l Toxicology Program, U.S. Dep't of Health & Human Servs. xii, 11, 16 (2012) (hereinafter "NTP Monograph") (attached as Ex. 6).

[7] *Id.* at 9.

[8] *Id.* at 17.

22. Lead can pass from a mother's lead stores and blood to her unborn baby, increasing the risk that the baby will be born too early or too small. Lead exposure has also been associated with an increased incidence of miscarriages and delays in the time to achieve pregnancy.[9] One case control study showed that the odds of miscarriage nearly doubled for every 5 μg/dL increase in maternal blood lead concentration.[10]

23. Children are particularly vulnerable to the neurotoxic effects of lead because their brain is rapidly growing during fetal development and early childhood. Rapidly growing tissues are more vulnerable to lead and other toxicants. Lead interferes with the formation of nerve connections, which are formed during brain development. Children under six years old also do not have a fully developed blood-brain barrier, which makes their brains more permeable to lead. Children are also more exposed to lead than adults because of their normal developmental behavior, including crawling and hand-to-mouth activity.

24. Childhood lead exposure has been associated with a wide array of

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[9] Marc Edwards, *Fetal Death and Reduced Birth Rates Associated with Exposure to Lead-Contaminated Drinking Water*, 48 Envtl. Sci. & Tech. 739, 739-46 (2014) (attached as Ex. 7); Motao Zhu et al., *Maternal Low-Level Lead Exposure and Fetal Growth*, 118 Envtl. Health Persp. 1471, 1471-75 (2010) (attached as Ex. 8).

[10] Victor H. Borja-Aburto et al., *Blood Lead Levels Measured Prospectively and Risk of Spontaneous Abortion*, 150 Am. J. Epidemiology 590, 590-97 (1999) (attached as Ex. 9).

irreversible neuropsychological and developmental effects. Increased levels of lead in blood can result in lower IQs, diminished academic achievement, increased risk of attention-related disorders, such as ADHD, and increased risk of problem behaviors, like conduct disorder. These associations remain even at low blood levels (below 5 µg/dL).[11] Blood lead levels of 10 µg/dL and lower are also associated with delayed onset of puberty, reduced growth, and impaired hearing.

25. Lead exposure is a strong predictor of behaviors linked with criminality, including impulsivity, hyperactivity, and aggressive behaviors.[12] Even low blood lead levels (below 5 µg/dL) have been associated with antisocial, disruptive, and violent behaviors, and with increased risk of criminal arrests.

26. Childhood lead exposure can have lifelong effects. Children with elevated blood lead levels may never reach the same peak cognitive ability later in life as children with less exposure to lead.[13] There is some evidence that lead exposure is a risk factor for developing Alzheimer's disease.[14]

27. Adults exposed to lead can also experience adverse health impacts. Adult lead exposure can result in increased blood pressure, or hypertension, and

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[11] NTP Monograph, *supra* note 6, at xviii (Ex. 6).

[12] Bruce P. Lanphear, *The Impact of Toxins on the Developing Brain*, 36 Annual Rev. Pub. Health 211, 221 (2015) (attached as Ex. 10).

[13] *Id.* at 218.

[14] *Id.* at 219.

chronic kidney disease. Adult lead exposure has been associated with increased risk of cardiovascular problems, decreased cognitive function, and increased incidence of tremors.[15]

Lead exposure in Flint

28. Many people in Flint already experience poor nutrition, poverty, and exposure to other toxins, like air pollution and tobacco smoke.[16] The new source of lead exposure in tap water will increase the overall risk that Flint residents, and children in particular, will compound the adverse effects of living in an impoverished community, including an increased risk of developing behavioral problems, ADHD, and reduction in learning abilities. The adverse effects of environmental toxins accumulate over time, chipping away at these children's chances to thrive.

29. It is deeply concerning that the proportion of children in Flint with elevated blood lead levels has increased from 2.4% to 4.9% since the City's water system began distributing water from the Flint River.[17] Given the temporal nature of the elevation in lead poisoning with the failure to use anti-corrosion control,

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[15] Simoni Triantafyllidou & Marc Edwards, *Lead (Pb) in Tap Water and in Blood: Implications for Lead Exposure in the United States*, 42 Crit. Rev. Envtl. Sci. & Tech. 1297, 1319 (2012) (attached as Ex. 11).

[16] Hanna-Attisha, *supra* note 4, at 286 (Ex. 5).

[17] *Id.* at 283.

most of this increase can be attributed to ingestion of contaminated tap water.

30. The first and most important step that must be taken to prevent further harms to the children and adults that reside in Flint is to reduce or prevent ongoing exposures to lead in drinking water. This means providing children and adults with a reliable source of clean drinking water. Eliminating lead hazards *before* exposure, known as primary prevention, is the only effective way to protect children from lead toxicity.

31. To help mitigate the effects of lead exposure in the Flint community, many other kinds of interventions are now required and will be needed for years to come. These include nutrition programs, high-quality childcare, early education programs, and developmental and behavioral assessments. But the first, critical step is to end exposure.

I declare under penalty of perjury that the foregoing is true and correct.

March 23, 2016

Bruce Perrin Lanphear, MD, MPH

Date

INDEX OF EXHIBITS

Exhibit	Description
1	Curriculum Vitae of Bruce P. Lanphear, M.D., M.P.H.
2	Ronnie Levin et al., *Lead Exposures in U.S. Children, 2008: Implications for Prevention*, 116 Envtl. Health Persp. 1285 (2008)
3	Patrick Levallois et al., *The Impact of Drinking Water, Indoor Dust and Paint on Blood Lead Levels of Children Aged 1–5 years in Montréal (Québec, Canada)*, 24 J. Exposure Sci. & Envtl. Epidemiology 185 (2014)
4	Michael W. Shannon & John W. Graef, *Lead Intoxication in Infancy*, 89 Pediatrics 87 (1992)
5	Mona Hanna-Attisha et al., *Elevated Blood Lead Levels in Children Associated With the Flint Drinking Water Crisis: A Spatial Analysis of Risk and Public Health Response*, 106 Am. J. Pub. Health 283 (2016)
6	Health Effects of Low-Level Lead, Nat'l Toxicology Program, U.S. Dep't of Health & Human Servs. (2012) (excerpted to include pages xv-18)
7	Marc Edwards, *Fetal Death and Reduced Birth Rates Associated with Exposure to Lead-Contaminated Drinking Water*, 48 Envtl. Sci. & Tech. 739 (2014)
8	Motao Zhu et al., *Maternal Low-Level Lead Exposure and Fetal Growth*, 118 Envtl. Health Persp. 1471 (2010)
9	Victor H. Borja-Aburto et al., *Blood Lead Levels Measured Prospectively and Risk of Spontaneous Abortion*, 150 Am. J. Epidemiology 590 (1999)

10 Bruce P. Lanphear, *The Impact of Toxins on the Developing Brain*, 36 Annual Rev. Pub. Health 211 (2015)

11 Simoni Triantafyllidou & Marc Edwards, *Lead (Pb) in Tap Water and in Blood: Implications for Lead Exposure in the United States*, 42 Crit. Rev. Envtl. Sci. & Tech. 1297 (2012)

EXHIBIT 1

CURRICULUM VITAE

Bruce Perrin Lanphear, MD, MPH

Office Address
Blusson Hall
8888 University Drive
Burnaby, BC V5A 1S6
Canada
E-mail: blanphear@sfu.ca

Home and Mailing Address
3415 Ash Street
Vancouver, BC, V5Z 3E5
TEL: (604) 873-6434
Cell: (778) 387-3939

Date of Birth: January 12th, 1963

Marital status: Married to Nancy Ebbesmeyer Lanphear, M.D., a developmental pediatrician

Children: Three children, Rachel (24), Ella (19) and Martha (17)

Specialty: Board Certified in General Preventive Medicine & Public Health

Employment

1984-1986	Paramedic, Jackson County Jail, Kansas City, Missouri
1988-1989	Physician, International Travel Clinic, University of Cincinnati, Cincinnati, Ohio
1988-1989	Staff Physician, Sexually Transmitted Disease Clinic, Cincinnati Public Health Department, Cincinnati, Ohio
1989-1992	Assistant Professor of Environmental Health, Associate Director, Medical Center Health Services, University of Cincinnati
1992-1997	Senior Instructor, Departments of Pediatrics and of Community & Preventive Medicine, University of Rochester School of Medicine.
1992-1994	National Research Scholar Award in General Pediatric Research, University of Rochester School of Medicine and Dentistry.
1992-1997	Assistant Professor, Department of Pediatrics and of Community & Preventive Medicine, University of Rochester School of Medicine.
1997-2002	Associate Professor, Department of Pediatrics, Children's Hospital Medical Center and the University of Cincinnati, Cincinnati, Ohio.
1997-2008	Director, General Pediatric Research Fellowship Training Program, Children's Hospital Medical Center and the University of Cincinnati.
1997-2008	Director, Children's Environmental Health Center, Children's Hospital Medical Center and the University of Cincinnati.
1997-2006	Associate Professor (Adjunct), Departments of Pediatrics and of Environmental Medicine, University of Rochester School of Medicine & Dentistry, Rochester, NY.
1998-2003	Associate Director for Research, Division of General & Community Pediatrics, Children's Hospital Medical Center.
2001-2002	Associate Professor (tenured), Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio.
2001-2004	Associate Professor (Adjunct), Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan.
2002-2008	Sloan Professor of Children's Environmental Health, Departments of Pediatrics and Environmental Health, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

2008-2012	Adjunct Professor of Pediatrics, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and the University of Cincinnati.
2008-	Professor of Children's Environmental Health, Faculty of Health Sciences, Simon Fraser University
2008-	Clinician Scientist, Child & Family Research Institute, BC Children's Hospital, University of British Columbia

Education

1980-1985	Bachelor of Arts in Biology
1980-1986	University of Missouri at Kansas City, Medical Degree (1986)
1986-1987	Internship, University of Arkansas for Medical Sciences, Little Rock, Arkansas
1987-1988	Tulane School of Public Health & Tropical Medicine Masters in Public Health & Tropical Medicine
1987-1989	General Preventive Medicine and Public Health Residency Tulane School of Public Health & Tropical Medicine
1992-1995	Fellowship in General Academic Pediatric Research University of Rochester School of Medicine, Rochester, NY

Awards and Honors

2011	Sterling Prize in Controversy, Simon Fraser University
2012	Research Integrity Award, International Society for Environmental Epidemiology
2013	Public Policy and Advocacy Award, Academic Pediatric Association
2015	Research Award, Academic Pediatric Association
2015	Confederation of Union Faculty Associations of British Columbia (CUFA-BC) Academic of the Year Award

Teaching Experience

1992-1997	Course Instructor, "Public Health & the Environment", Department of Community & Preventive Medicine, The University of Rochester School of Medicine and Dentistry. A required course for MPH students taught annually.
1997-2008	Founding Director, NIH-funded, General Academic and Community Pediatric Research Fellowship Training Program, Cincinnati Children's Hospital Medical Center. This interdisciplinary, research training program included pediatricians, psychologists and epidemiologists. It was the first training program in Children's Environmental Health.
1998-2008	Course Co-Instructor, "Children's Health & the Environment", Department of Environmental Health, The University of Cincinnati School of Medicine. A course taught every other year to MPH, PhD and postdoctoral trainees in medical subspecialties.
2008-	Course Instructor, "Children's Health and the Environment". A course taught annually to undergraduate students at Simon Fraser University.
2011-	Course Instructor, "Plagues, Pollutants and Poverty: The Origins and Evolution of Public Health". A course taught annually to undergraduate students at Simon Fraser University.

Committee and Community Involvement

1993-1997	Lead Poisoning Prevention Task Force, Monroe County Health Department.
1994-1997	Investigational Review Board, Rochester General Hospital
1995-	Scientific Consultant, National Center for Healthy Housing, Columbia, Maryland.
1996-1997	Member, New York State Task Force on Environmental Neurotoxins, University of Rochester School of Medicine
1996-2001	Member, National Institute for Environmental Health Sciences Grant Review Committee for Community-Based Interventions (FG)
1996-1998	Chairman, U.S. Department of Housing and Urban Development Committee on Lead-Contaminated House Dust
1998	Member, Review Group for National Research Service Awards, Health Resources and Services Administration
1998-2000	Member, Cincinnati Board of Health, Cincinnati, Ohio.
1998-2001	Member, Science and Research Work Group, Office of Children's Health Protection Advisory Committee, U.S. EPA
1998-2000	Member, Cincinnati Lead Poisoning Prevention Advisory Task Force, Cincinnati, Ohio.
1999	Member, K23 Grant Review Committee, National Institute for Environmental Health Sciences, August 1999
1999	Member, Expert Panel on Soil Pica Behavior, Agency for Toxic Substance Disease Registry, June 7th-8th, Atlanta, Georgia
2000	Member, Panel on Health Disparities: Linking Biological and Behavioral Mechanisms with Social and Physical Environments, National Institute for Environmental Health Sciences, July 14-15th
2000-2002	Member, Workshop on Assessing Environmental Exposures to Children, U.S. Environmental Protection Agency, July 26-27th
2000-2004	Member, Children's Environmental Health Project, AAP's Child Health Research Center, Rochester, NY.
2001	Participant, "ILSI Workshop to Develop a Framework for Assessing Risks to Children from Exposure to Environmental Agents", Stowe, Vermont, July 30 to August 2nd 2001.
2001	Senate Testimony, "Ensuring that Children with Dangerous Levels of Lead in their Blood Receive Care as Early as Possible". Subcommittee on Housing and Transportation of the Committee on Banking, Housing and Urban Affairs, 107th U.S. Congress, November 13th, 2001.
2001	Reviewer, National Research Council, National Academy of Science Update of the 1999 Arsenic in Drinking Water Report
2001-2003	Member, Expert Panel on Children's Health and the Environment, North American Commission for Environmental Cooperation
2002-	Member, Scientific Advisory Board, Scientist Communication Network.
2003	Member, "Herculaneum Health Study Workshop" Agency for Toxic Substance Diseases Registry, May 22nd to 23rd, 2003
2003-2004	Panel Member, "Lead Poisoning in Pregnant Women", Mt. Sinai for Children's Health and the Environment, New York, NY
2003	Member, "Invitational Workshop on a proposed American Family Study" National Human Genome Research Institute, December 1st to 3rd, 2003.
2004-2006	Member, Committee on "Ethical Consideration for Research on Housing-Related Health-Hazards involving Children", National Research Council and the Institute of Medicine, The National Academies
2004	Congressional Testimony, "Tapped Out? Lead in the District of Columbia and the Providing of Safe Drinking Water", Subcommittee on Environment and Hazardous

	Materials of the Committee on Energy and Commerce, U.S. House of Representatives, 108th Congress, July 22nd, 2004
2005	Reviewer, "Superfund and Mining Megasites – Lessons from the Couer d" Alene River Basin", National Research Council, The National Academies.
2005	Ad Hoc Member, NIEHS Board of Scientific Counselors Review of the Epidemiology Branch, April 3rd to April 5th, 2005
2005	Senate Briefing, "The Connection of Environmental Chemicals and Learning Disabilities", The Relationship Between Chemical Exposures and Incidence of Learning and Other Developmental Disabilities, U.S. Senate, May 10th, 2005
2006	Invited Participant, NIEHS Strategic Planning Forum, National Institute for Environmental Health Sciences, Chapel Hill, North Carolina, October 17-18th, 2006.
2006-2008	Member, U.S. EPA's Clean Air Scientific Advisory Committee Lead Review Panel.
2006-2008	Member, National Children's Study Steering Committee, NICHD
2006	Invited Participant, "How Does Housing Affect Health Outcomes of Children?", MacArthur Foundation, Chicago, Illinois, June 21st-22nd, 2006.
2006- 2010	Member, External Scientific Advisory Committee, Richmond Center for Excellence in Tobacco Research, American Academy of Pediatrics.
2007	Testimony, Vermont State Legislature, "The Lingering Legacy of Lead Toxicity", Montpelier, Vermont, February 1st, 2007
2007	Testimony, Connecticut State Legislature, "The Legacy of Lead Toxicity", Hartford, Connecticut, March 14th, 2007. (PG)
2007	Invited Testimony, United States Senate Hearing, "Lead and Children's Health". Committee on Environmental and Public Works, October 18th, 2007
2007-2008	Member, Committee on "Committee on Contaminated Drinking Water at Camp Lejeune", National Research Council, The National Academies.
2008	Member, Expert Panel on Health and the Environment, Statistics Canada, Ottawa, Canada
2008-	Member, Alliance for the Global Elimination of Lead Paint, Intergovernmental Forum on Chemical Safety (IFCS), World Health Organization
2008-2009	Reviewer, Toxicological Review and Recommended Toxicological Reference Values for Environmental Lead Exposure in Canada, Health Canada
2009-2013	Scientific Advisor, Canada Lead Study funded by Health Canada (Patrick Levallois, Principal Investigator).
2009-2014	Board Member, Barro Sin Plomo
2009-2010	Member, Health and Environment Experts Advisory Group of the Canadian Longitudinal Study on Aging, Canadian Institutes of Health Research
2010-2012	Member, US Environmental Protection Agency Science Advisory Board for Evaluating Dust Lead Standards
2010-2013	Advisor, Canada Environmental Health Law and Canadian Partnership for Children's Health and Environment Retrofit Project
2010-2012	Member, Physicians Advisory Panel, Canada Health Measures Survey
2010	Invited Testimony, United States Senate Hearing, "Research on Environmental Health Factors with Autism and Neurodevelopmental Disorders", August 3rd, 2010
2010	Member, Joint FAO/WHO Expert Panel for Toxicological and Health Review of Bisphenol A
2010-	Board Member, Global Community Monitoring, Oakland, California
2010-	Chairman, Scientific Advisory Committee for Dartmouth University's Program in Children's Health and the Environment
2011-	Member, American Academy of Pediatrics Executive Council on Environmental Health
2011-2012	Member, US Environmental Protection Agency Science Advisory Board for Evaluating Hazards of Partial Water Line Replacement

2011	Invited Testimony, Special Committee on Cosmetic Pesticides, Legislative Assembly, Province of British Columbia, October 7th, 2011
2011-2012	Member, Panel on Health Effects of Low-level Lead, Office of Health Effects, National Toxicology Program of the National Institutes of Environmental Health Sciences, November 17-18 h, 2011
2012-	Member, Expert Advisory Committee, Canada Health Measures Survey
2012-	Member, Environmental Defence Fund Science Advisory Committee on Toxics
2015	Reviewer, Review of Clinical Guidance for the Care of Health Conditions Identified by the Camp Lejune Legislation, Institute of Medicine, The National Academies
2016-	Member, The Lancet Commission on Pollution, Health & Development

Editorial Boards

2000-	Assistant Editor, *Environmental Research*
2000-2008	Deputy Editor, *Public Health Reports*
2004	Associate Editor, *Pediatrics* supplement on Children's Environmental Health
2004-	Editorial Board Member, *PLoS Medicine*
2005-2014	Editorial Board Member, *Breastfeeding Medicine*
2007-	Editorial Board Member, *Environmental Health*
2008-2012	Editorial Review Board Member, *Environmental Health Perspectives*
2012-	Associate Editor, *Environmental Health Perspectives*

Societies and Organizations

1989-2008	American Public Health Association
1996-	Academic Pediatric Association
1997-2012	American Association for the Advancement of Science
2000-2008	Society for Pediatric Research
2001-2008	American Pediatric Society
2001-	Specialty Fellow, American Academy of Pediatrics
2006-	Fellow, Collegium Ramazzini
2006-	Member, International Society for Environmental Epidemiology
2008-	Founding Member, International Society for Children's Health & the Environment
2011-	Secretary and Treasurer, International Society for Children's Health & the Environment
2012-	Member, International Society for Exposure Science

Video and Website Production

1. Canadian Environmental Health Atlas: A portal to discover the promise of environmental health.
2. Shifting the curve: the impact of toxins on ADHD in U.S. children
3. Latency period: Asbestos exposure and the development of malignant mesothelioma
4. Little things matter: The impact of toxins on the developing brain
5. Little things matter: The impact of toxins on preterm birth

Original Research

1. Lanphear BP. Deaths in Custody. American Journal Forensic Medicine & Pathology 1987;8:299-301.
2. Lanphear BP, Snider DE. Myths of Tuberculosis. J Occ Med 1991;33:501-504.

3. Linnemann CC Jr, Cannon C, DeRonde M, Lanphear BP. Effect of educational programs, rigid sharps containers, and universal precautions on reported needle-stick injuries in healthcare workers. Infection Control Hospital Epidemiology 1991;12:214-20.
4. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. Journal Occupational Med 1992;34:718-721.
5. Lanphear BP, Linnemann CC Jr, Cannon CG, DeRonde MM. Decline of clinical hepatitis B in workers at a general hospital. Clinical Infectious Disease 1993:11:10-14.
6. Lanphear BP, Linnemann CC Jr, Cannon C, DeRonde MM, Pendy L, Kerly L. Hepatitis C virus infection in health care workers. Infection Control Hospital Epidemiology 1994;15:745-750.
7. Lanphear BP, Emond M, Jacobs DE, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S. A side-by-side comparison of dust collection methods for sampling lead-contaminated house-dust. Environmental Research 1995;68:114-123.
8. Lanphear BP, Winter NL, Apetz L, Eberly S, Weitzman M. A randomized trial of the effect of dust control on children's blood lead levels. Pediatrics 1996;98:35-40.
9. Christy C, Pulcino M, Lanphear BP, McConnochie K. Screening for tuberculosis infection in urban children. Arch Pediatrics Adolescent Med 1996;150:722-726.
10. Lanphear BP, Weitzman M, Eberly S. Racial differences in environmental exposures to lead. American Journal of Public Health 1996;86:1460-1463.
11. Lanphear BP, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S, Emond M, Matte TD. Lead-contaminated house dust and urban children's blood lead levels. American Journal of Public Health 1996;86:1416-1421.
12. Lanphear BP, Byrd RS, Auinger P, Hall CB. Increasing prevalence of recurrent otitis media among children in the United States. Pediatrics 1997. http//www.pediatrics.org/cgi/contents/full99/3/e1.
13. Emond MJ, Lanphear BP, Watts A, Eberly S for the Rochester Lead-in-Dust Study Group. Measurement error and its impact on the estimated relationship between dust lead and children's blood lead. Environmental Research 1997;72:82-92.
14. Lanphear BP, le Cessie S, Atkinson WL, Watelet L. Association of live births and the resurgence of measles. International Journal Epidemiology 1997;26:204-211.
15. Rust SW, Burgoon DA, Lanphear BP, Eberly S. Log-additive versus log-linear analysis of lead-contaminated house dust and children's blood lead levels: Implications for residential dust-lead standard. Environmental Research 1997;72:173-184.
16. Lanphear BP, Roghmann KJ. Pathways of lead exposure in urban children. Environmental Research 1997;74:67-73.

17. Lanphear BP, Byrd RS, Auinger P, Schaffer S. Community characteristics associated with elevated blood lead levels in children. Pediatrics 1998;101:264-271.
18. Lanphear BP, Rust SW, Burgoon DA, Eberly S, Galke W. Environmental exposures to lead and urban children's blood lead levels. Environmental Research 1998;76:120-130.
19. Lanphear BP. The paradox of lead poisoning prevention. Science 1998;281:1617-1618.
20. Lanphear BP, Hall CB, Black J, Auinger P. Risk factors for the early acquisition of HHV-6 and HHV-7 infection in children. Pediatric Infectious Disease Journal 1998;17:792-795.
21. Lanphear BP, Matte TD, Rogers J, Clickner R, Dietz B, Bornschein RL, Succop P, Mahaffey KR, Dixon S, Galke W, Rabinowitz M, Farfel M, Rohde C, Schwartz J, Ashley P and Jacobs DE. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels: A pooled analysis of 12 epidemiologic studies. Environmental Research 1998;79:51-68.
22. Marron R, Lanphear BP, Kouides R, Dudman L, Manchester R, Christy C. Efficacy of informational letters on Hepatitis B immunization rates in university students. J Am College Health 1998;47:123-127.
23. Howard CR, Howard FM, Lanphear BP, deBlieck EA, Eberly S, Lawrence RA. Effect of early pacifier use on breastfeeding duration. Pediatrics 1999;103. http//www.pediatrics.org/cgi/contents/full103/3/e33.
24. Lanphear BP, Howard CR, Eberly S, Auinger P, Kolassa J, Weitzman M, Alexander K, Schaffer S. Primary prevention of childhood lead exposure: A randomized trial of dust control. Pediatrics 1999;103:772-777.
25. Moss ME, Lanphear BP, Auinger P. Association of dental caries and blood lead levels among the U.S. population. JAMA 1999;281:2294-2298.
26. Howard CR, de Blieck EA, ten Hoopen C, Howard F, Lanphear BP, Lawrence RA. Physiologic stability of newborns during cup and bottle-feeding. Pediatrics 1999;104:1204-1207.
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Letters

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Presentations

1. “Biologic Hazards to Health Care Personnel in the Workplace”. University of Cincinnati, Cincinnati, Ohio, September 26, 1990.
2. “Common Misconceptions about Tuberculosis”. American Lung Association, St. Elizabeth’s Hospital, Belleville, IL, March 19, 1991.
3. “Prevention and Control of Infectious Disease in Health Care Workers”. Miami Valley Hospital, Dayton, OH, September 5, 1991.
4. “Transmission of Hepatitis B Virus Infection in Health Care Workers”. Ohio University, Athens, Ohio, March 21, 1992.

5. “Universal Immunization Against Hepatitis B Virus”. Grand Rounds, Dayton Children’s Hospital, May 1992, Dayton, Ohio.
6. "Correlation of Blood Lead Levels and Dust Lead Levels Using Three Dust Collection Methods. Environmental Protection Agency, Research Triangle, N.C., January 20,1994.
7. "Relation of Lead-Contaminated House Dust and Blood Lead Levels in Urban Children" Environmental Protection Agency, Washington, D.C., February, 1994.
8. "Lead-Contaminated House Dust and Blood Lead Concentrations in Children", Society for Pediatric Research, Seattle, Washington May 5, 1994.
9. "EPA Health-Based Standards for Soil and Dust". Alliance to End Childhood Lead Poisoning, Washington, D.C., May 17, 1994.
10. "Epidemiology of Tuberculosis in Health Care Settings". University of Cincinnati, Cincinnati, OH, August 19, 1994.
11. "A Side-by-Side Comparison of Sampling Methods for Lead-Contaminated House Dust". American Public Health Association, Washington, D.C., November 1, 1994.
12. “Trends in Childhood Exposure to Lead: Implications for Prevention”. University of Rochester, Pediatric Grand Rounds, February 15, 1995.
13. “Childhood Exposure to Lead”. Visiting Professor, Nazareth College, Rochester, New York, March 24, 1995.
14. “Transmission and Control of Infections in Health Care Workers”. (Moderator & Speaker) American College of Occupational Environmental Medicine, Las Vegas, Nevada, May 4, 1995.
15. “Lead Exposure Prevention Research at the University of Rochester”. New England Lead Conference, Kennebunkport, Maine, August 3, 1995.
16. “Prevention of Childhood Lead Exposure”. 1st Annual Midwest Conference on Childhood Lead Poisoning Prevention, Kansas City, MO, September 10-11, 1995.
17. “Childhood Lead Exposure: Implications for Occupational Health”. National Institute for Occupational Safety and Health, Cincinnati, OH, May 10, 1996.
18. “Community Characteristics and Children’s Blood Lead Concentrations”. American Public Health Association, New York City, NY, November 19, 1996.
19. “Evolution of a Disease: The Science of Childhood Lead Exposure Prevention.” American Public Health Association, New York City, NY, November 18, 1996.
20. “Childhood Lead Exposure: A Local and National Perspective.” Occupational Medicine Grand Rounds, University of Rochester, January 2, 1997.
21. “Prevention of Childhood Lead Exposure: The U.S. Experience”. (Keynote) University of the West Indies and Pan American Health Organization, Kingston, Jamaica, January 23, 1997

22. "Lead-Contaminated House Dust and Children's Blood Lead Levels". (Keynote Presentation) Look Out for Lead Conference, Madison, WI, May 22, 1997.
23. "Primary Prevention of Childhood Lead Exposure: A Randomized Trial of Dust Control". American Public Health Association, Indianapolis, November 13, 1997.
24. "Evolution of a Disease: Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Medical University of South Carolina, Charleston, SC, March 20, 1998.
25. "The Science of Childhood Lead Exposure Prevention." Tulane/Xavier Center for Bioenvironmental Research, New Orleans, May 4-5th, 1998.
26. "Lead Hazard Control Research" Conference on Linking Health, Housing & Environment, Centers for Disease Control, Department of Housing and Urban Development, National Institutes of Health, Phoenix, Arizona, June 21-24, 1998.
27. "A Randomized Trial of Dust Control to Prevent Childhood Lead Exposure." Presenter and Co-chairman, Section on Heavy Metals, 1st International Conference on Children's Environmental Health, Amsterdam, The Netherlands, August 11-13th, 1998.
28. "Prevention of Childhood Lead Exposure: A Critique of the EPA's Proposed Residential Lead Standard". Office of Children's Health Protection, U.S. Environmental Protection Agency, Washington, D.C., November 5, 1998.
29. "Science and Policy of Lead Poisoning Prevention in the United States". Nicholas School of the Environment, Duke University, Durham, North Carolina, February 22, 1999.
30. "Behaviors in Early Childhood and Exposure to Environmental Toxins". (invited) Pediatric Environmental Health Conference, San Francisco, CA May 4, 1999.
31. "Patterns of Lead Exposure in Early Childhood". International Conference on Lead Exposure, Reproductive Toxicity and Carcinogenicity, Gargnano, Italy, May 7, 1999.
32. "Adverse Effects of Blood Lead Concentrations <10 μg/dL" (Invited), 17h International Conference Neurotoxicology Conference, Little Rock, Arkansas, October 17-20, 1999.
33. "Emerging Research and Implications for Prevention of Childhood Lead Exposure" (Invited), 2nd Annual Syracuse Lead Conference, Syracuse, New York October 27th, 1999.
34. "Prevention of Lead Poisoning in Children" Sierra Club, Omaha, NE, November 16th, 1999.
35. "Children's Environmental Health: A Focus on Residential Hazards" Department of Pediatrics, University of Nebraska Hospital, November 17th, 1999.
36. "Effectiveness of Lead Hazard Controls", New England Lead Conference, New Hampshire, Tufts University School of Medicine, April 25, 2000.
37. "Subclinical Lead Toxicity in U.S. Children and Adolescents", Pediatric Academic Societies, Boston, MA, May 15, 2000.

38. "Contribution of Residential Exposures to Asthma in U.S. Children and Adolescents", Pediatric Academic Societies, Boston, MA, May 16, 2000.
39. "The Effect of Soil Abatement on Blood Lead Concentration in Children living near a former Smelter and Milling Operation" (invited). Coeur d'Alene, Idaho, May 24, 2000.
40. "The Paradox of Lead Poisoning Prevention" (invited). National Institute of Justice, Washington, D.C., July 18th, 2000.
41. "Evolution of a Disease: Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Children's Hospital Medical Center, Cincinnati, Ohio, August 22, 2000.
42. "Children's Environmental Health: A Focus on Residential Hazards" Pediatric Grand Rounds, Department of Pediatrics, University of Rochester School of Medicine, Rochester, NY, September 20th, 2000.
43. "Prevention of Lead Poisoning in Childhood" 7th Annual Childhood New York State Lead Poisoning Prevention Conference, Purchase College, NY, September 29, 2000.
44. "Excavating the Enigmas of Childhood Lead Exposure". Department of Environmental and Occupational Medicine, Harvard University School of Public Health, Boston, MA, October 16th, 2000.
45. "Contribution of Residential Exposures to Asthma". Eliminating Childhood Lead Poisoning: Our Challenge for the Decade, Centers for Disease Control and the U.S. Department of Housing & Urban Development, December 11h, 2000.
46. "Setting Research Priorities for the Decade". (Moderator & Speaker) Eliminating Childhood Lead Poisoning: Our Challenge for the Decade, Centers for Disease Control and the U.S. Department of Housing & Urban Development, December 13th, 2000.
47. "Evolution of a Disease: Prevention of Childhood Lead Exposure." (Keynote Presentation) Look Out for Lead Conference, Madison, WI, April 12, 2001.
48. "Environmental Lead Exposure and Children's Intelligence at Blood Lead Concentrations below 10 μg/dl." APA Presidential Plenary Session, Pediatric Academic Society Meeting, Baltimore, MD, April 30, 2001.
49. "Elimination of Childhood Lead Exposure: Obstacles & Opportunities" (Plenary). National Housing Conference and Exposition, New Orleans, LA, May 16th, 2001.
50. "Prevention of Childhood Lead Exposure: A Public Health Perspective" (Keynote Presentation). Philadelphia Health Department, Philadelphia, PA, May 23rd, 2001.
51. "Evolution of a Disease: Prevention of Childhood Lead Exposure." (Keynote Presentation), Charles Drew University, Los Angeles, California, October 22nd, 2001.

52. "Primary Prevention of Childhood Lead Exposure" (Keynote Presentation), Midwest Regional Lead Conference, Pittsburgh PA, October 29th, 2001.
53. "Prevention of Childhood Lead Exposure: Shifting to Primary Prevention" (Keynote Presentation), Indiana Department of Health, Lead-Safe Conference, November 7th, 2001.
54. "A Strategy for Primary Prevention of Childhood Lead Exposure" A testimony to Housing and Transportation Subcommittee, U.S. Senate, Washington, D.C., November 13, 2001.
55. "Ethical issues of Environmental Research involving Children" (moderator and speaker). Panelists were Jeffrey Kahn, Ph.D., and Leonard Glantz, J.D., Raleigh-Durham, North Carolina, NIEHS Conference of Children's Environmental Health Centers, January 23, 2001.
56. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Omaha Children's Hospital, Omaha, Nebraska, March 1, 2002.
57. "Racial Disparities in Children due to Environmental Hazards" Ohio Commission on Minority Health, Columbus, Ohio March 27, 2002.
58. "Prevention of Childhood Lead Exposure in a Former Mining Community" Tar Creek, Oklahoma, April 4, 2002.
59. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Hasbro Children's Hospital, Brown University, Providence Rhode Island, May 17, 2002.
60. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Dayton Children's Hospital, Wright University, Dayton, Ohio May 22, 2002.
61. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." International Lead Congress, Washington, DC, June 3rd, 2002.
62. "Residential Hazards: A Neglected Health Problem" Agency for Toxic Substances Disease Registry, Centers for Disease Control and Prevention, Atlanta, Georgia, August 19th, 2002.
63. "Control of Residential Exposures to Environmental Neurotoxins" National Center for Healthy Homes (Moderator and Speaker), Annapolis, VA, November 7th, 2003.
64. "The Promises and Potential Pitfalls of Primary Lead Poisoning Prevention" Purchase College, 9th Annual Childhood New York State Lead Poisoning Prevention Conference, Purchase College, New York,, October 4th, 2002.
65. "Evolution of a Disease: the Science and Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Syracuse, NY, October 9th, 2002.
66. "Evolution of a Disease: the Science and Prevention of Childhood Lead Exposure." University of Texas at El Paso, El Paso, Texas January 29th, 2003.
67. "Childhood Lead Poisoning" Introduction to Children's Environmental Health, Seattle, Washington, Pediatric Academic Society, May 3rd, 2003.

68. "The Legacy of Lead: Childhood Lead Poisoning in the 21st Century". Chicago Lead Summit, Chicago, Illinois, May 28th, 2003.
69. "The Legacy of Lead: Childhood Lead Poisoning in the 21st Century". Case Western Reserve University, Cleveland, Ohio, June 3rd, 2003.
70. "Housing and Children's Health", Sprawl: The impact on vulnerable populations, University of Cincinnati College of Medicine, Cincinnati, Ohio, July 8th, 2003.
71. "Trials and Tribulations of Protecting Children from Environmental Toxins". Duke University, Nicholas School of the Environment, Durham, NC, November 6th, 2003.
72. "Adverse Effects of Fetal and Childhood Exposures to Prevalent Toxins" Midwest Critical Regional Neonatology Conference, Covington, KY, November 14th, 2003.
73. "Control of Residential Hazards in Children" American Public Health Association, San Francisco, CA, November 18th, 2003.
74. "Low-Level Exposure to Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis". 21st International Neurotoxicology Conference, Honolulu, Hawaii, February 11th, 2004.
75. "Trials and Tribulations of Protecting Children from Environmental Hazards" Workshop on Ethical Issues on Children's Environmental Health, Children's Environmental Health Network, Washington, D.C. March 5, 2004.
76. "Low-Level Exposure to Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis", Pediatric Academic Societies Annual Meeting. Pediatric Research 2004;55:163A.
77. "The Impact of the Environment on Children's Health" Bob Smith Endowed Lecture, Department of Pediatrics, First Gulf Coast Children's Environmental Health Symposium, Baylor University, Houston, Texas.
78. "The Search for Environmental Causes of Learning Disabilities, Learning Disabilities Initiative, Baltimore, MD, May 18th, 2004.
79. "Residential Hazards in Children: A Neglected Public Health Problem", Pediatric Grand Rounds, Boston Medical Center, Department of Pediatrics, Boston University Medical Center, Boston, MA, May 20th, 2004.
80. "Residential Hazards in Children" "Healthier Homes, Stronger Families: Public Policy Approaches to Healthy Housing", National Center for Healthy Housing, Washington, D.C., June 2nd, 2004.
81. "Fetal and Early Childhood Exposures to Prevalent Toxins" Pediatric Grand Rounds, Ste. Justine Children's Hospital, University of Montréal, Montreal, Canada, June 16th, 2004.

82. "Childhood Exposure to Lead-Contaminated Soil: A Problem of the Past or a Problem from the Past?" National Academy of Science Committee on Superfund Site Assessment and Remediation in Coeur d'Alene River Basin", June 17th, 2004, Coeur d'Alene, Idaho.
83. "The Legacy of Lead" (Keynote Speaker). Chicago Lead Summit, Region V EPA Headquarters, September 15th, 2004.
84. "A Tale of Two Toxins: Children's Exposure to Tobacco and Lead" (with Michael Weitzman), The American Academy of Pediatrics, San Francisco, CA, October 10th, 2004.
85. "A Legacy of Childhood Lead Poisoning" University of Washington, Seattle, Washington, October 30, 2004.
86. "Protecting Children from Environmental Toxins", Pediatric Grand Rounds, Seattle Children's Hospital, Seattle Washington, March 10th, 2005.
87. "The Science and Politics of Childhood Lead Poisoning", Northwest Pediatric Environmental Health Conference, University of Washington, Seattle, Washington, March 11th, 2005.
88. "The Effects of Low-level Exposure to Environmental Toxins during Fetal Development and Early Childhood", Children's' Hospital of Fudan University, Shanghai International Pediatric Forum, Shanghai, China, June 16th to 18th, 2005.
89. "The Role of Biomarkers in Revealing Genetic and Environmental Influences of Disease and Disability" Psychiatry Grand Rounds, University of Cincinnati, February 8th, 2006.
90. "Trials and Tribulations of Protecting Children from Environmental Hazards: Ethical Issues", Johns Hopkins University of Medicine, March 17th, 2006.
91. "Key Elements of a Primary Prevention Strategy for Lead Poisoning", Albany Law School, Union University, Albany, New York, March 16th, 2006.
92. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold"", Case Western Reserve University, City Club of Cleveland, Cleveland, OH March 4th, 2006.
93. Integrating Genetic and Environmental Influences in Pediatric Research" (Moderator and Speaker), Pediatric Academic Societies, San Francisco, CA, April 30th 2006.
94. "Ethical Issues in Housing Health Hazard Research Involving Children" (Topic Symposia) Pediatric Academic Societies, San Francisco, CA, May 2nd 2006.
95. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold"", International Workshop on Neurotoxic metals: from Research to Prevention, University of Brescia, Italy, June 17th, 2006.
96. "Efficacy of HEPA-CPZ Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms", International Society for Environmental Epidemiology, Paris France, September 6th, 2006.
97. "Protecting Children from Environmental Toxins", Region VIII Children's Environmental Health Summit, Vail, Colorado September 20th, 2006.

98. "Integrating Genetic and Environmental Biomarkers in Pediatric Epidemiology", Visiting Professor, Simon Fraser University and University of British Columbia, Vancouver, British Columbia, October 19th-20th, 2006.
99. "The Legacy of Lead", Indiana Lead Conference, Indianapolis, Indiana, October 24, 2006.
100. "Ethical dilemmas in Children's Environmental Health", Seminar Series in Ethics of Toxicology, University of Champagne-Urbana, Champagne, Illinois, November 19th, 2006.
101. "Low-Level Lead Toxicity: Implications for Prevention"", WHO Informal Workshop on Lead, University of Munich, Germany, November 30th, 2006.
102. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold"", National Environmental Public Health Conference, National Centers for Disease Control, Atlanta, Georgia, December 4th, 2006.
103. "The Epidemiologic Conquest of Childhood Lead Toxicity: A Pyrrhic Victory". NIEHS Workshop on Children's Environmental Health Research: Past, Present and Future. January 22nd, 2007.
104. "Linking Low-level Exposures to Environmental Toxicants with ADHD". Duke Integrated Toxicology and Environmental Health Program Symposium on Developmental Neurobehavioral Disabilities and Toxic Exposures, March 23, 2007, Durham, North Carolina.
105. "Using Biomarkers to Link Environmental Influences with Disease and Disability", The Channing Laboratory, Harvard University, Boston, Massachusetts, April 4th, 2007.
106. "The Lingering Legacy of Lead Toxicity". Grand Rounds, Department of Pediatrics, St. Louis Children's Hospital, St. Louis University, St. Louis, Missouri, April 11th, 2007.
107. "Protecting Children from Environmental Toxicants", United States Council of Catholic Bishops, Washington, D.C., April 30th, 2007.
108. "Efficacy of HEPA-CPZ Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms", Pediatric Academic Societies, APA Presidential Platform Plenary Session, Toronto, Canada, May 7th, 2007.
109. "The Lingering Legacy of Lead Toxicity" Grand Rounds, Department of Pediatrics, Omaha Children's Hospital, University of Nebraska, Omaha, Nebraska, April 11th, 2007.
110. "Linking Low-level Neurotoxicant Exposures of the Developing Brain to Learning and Behavioral Problems." International Conference on Developmental Programming and Effects of Environmental Toxicants in Human Health and Disease, Faroe Islands, May 20th, 2007.
111. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson", National Policy Consultation Series on Children's Health and Environment, Moncton, New Brunswick, Canada, May 31, 2007.

112. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" Occupational and Environmental Health Seminar Series, Health Canada, Ottawa, Canada, June 6th, 2007.
113. "Linking Low-Level Lead Exposure with Child and Adolescent Psychopathology", 13th Annual International Society for Research in Child and Adolescent Psychopathology, London, England, June 19th, 2007.
114. "The Legacy of Lead Toxicity". Pediatric Grand Rounds, New York Presbyterian Hospital-Weill Cornell Medical Center, September 18th, 2007.
115. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". Pediatric Grand Rounds, Children's Hospital at Dartmouth, Dartmouth Medical School, September 19th, 2007.
116. "The Legacy of Lead Toxicity: Effects of Childhood Lead Exposure in Children, Adolescents and Adults". Mid-America Conference, Philadelphia, Pennsylvania, October 4th, 2007.
117. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" International Society for Exposure Analysis (invited plenary session), Raleigh-Durham, North Carolina, October 17th, 2007.
118. The Global Elimination of Lead Toxicity: A Focus on Housing." National Institute of Public Health, Rennes, France, October 22nd, 2007.
119. Linkage of Environmental Lead Exposure with Psychopathology in Children and Adolescents" Ramazzini Collegium, Carpi, Italy, October 25th, 2007.
120. "Linking Exposures to Environmental Toxicants with Child and Adolescent Psychopathology", Symposium on Environmental Toxicity and the Brain, University of Toronto, Toronto, Canada, December 7th, 2007.
121. "Linking Exposures to Environmental Toxicants with Child and Adolescent Psychopathology." Pediatric Grand Rounds, Rochester General Hospital and Strong Memorial Hospital, Rochester, New York, April 1&2, 2008.
122. "Rochester's Role in the Ongoing Elimination of Childhood Lead Toxicity." Beaven Lecture, Rochester Academy of Medicine, Rochester, New York, April 1, 2008.
123. "The Lingering Legacy of Lead Toxicity: Lansing Legacy." Michigan's Conference for Lead Safe & Healthy Homes, East Lansing, MI, April 22, 2008.
124. First Annual Controversies in Pediatric Environmental Health, "Should the Centers for Disease Control Lower the Blood Lead Level of Concern". A debate by Bruce Lanphear and George G. Rhoads (James Sargent, Moderator). Pediatric Academic Societies Meeting, Honolulu, Hawaii, May 2nd, 2008.

125. “Linking Exposure to Environmental Toxicants with Psychopathology in Children and Youth”. Visiting Professor, Alberta Child and Youth Network, Calgary Children’s Hospital, Calgary, Alberta. May 13th-15th, 2008.
126. Lead Toxicity and the Teenage Brain”, Youth Exploring Science Program, St. Louis Science Center, St. Louis, Missouri, June 30th, 2008.
127. “The Legacy of Childhood Lead Toxicity”. Health Canada, Ottawa, Canada, October 6th, 2008.
128. “Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson”. The 2008 Rachel Carson Legacy Conference: Green Chemistry – Solutions for a Healthy Economy, Duquesne University, Pittsburgh, Pennsylvania, September 20 h, 2008.
129. “Trials and Tribulations of Protecting Children from Environmental Hazards”, Ethics in Toxicology Seminar Series, University of Champagne-Urbana, Champagne, Illinois, September 22nd, 2008.
130. “Industry’s Influence on the Prevention of Childhood Lead Poisoning.” In: Symposia on Insulating Environmental Health Research from Conflicting Interests. International Society for Environmental Epidemiology Annual Meeting, Pasadena, California, October 14th, 2008.
131. “The Lingering Legacy of Lead Toxicity: Implications for Research and Policy on Other Environmental Toxicants”. (Keynote Presentation) BC Environmental and Occupational Health Research Network, Vancouver, BC, November 7th, 2008.
132. “Effects of Environmental Toxicants on Children’s Development”. DB-PREP Course, American Academy of Pediatrics, Atlanta, Georgia, December 5th, 2008.
133. “Linking Low-level Environmental Toxicants with New Morbidities of Childhood". BC Children's Grand Rounds, British Columbia, Vancouver, February 6th, 2009.
134. "Using Biomarkers to Link Exposures with Disease and Disability in Children". Workshop on Physical and Chemical Exposures in Canadian Cohort Studies, Canadian Institute of Health Research and Health Canada, February 8th-9th, 2009.
135. "How Dangerous Is Lead In Drinking Water?" An interview on "Around The Water Cooler" with Werner Troesken and Bruce Lanphear. February 18th, 2009.
136. “Linking Environmental Toxicants with ADHD in Children” (invited), Learning Disabilities Association Annual Meeting, February 25th, Salt Lake City, Utah.
137. “The Lingering Legacy of Lead Toxicity”, Norfolk Children’s Hospital, April 30th, 2009, Norfolk Virginia.
138. Second Annual Controversies in Pediatric Environmental Health Debate, “Should Pediatricians Advise Parents to Feed their Children Organic Foods?” A debate by Joel Forman and Janet

Silverstein (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Baltimore, MD, May 4th, 2009.

139. "A Pattern of Pathology: The Population Impact of Environmental Toxicants on Health". Workshop on Endocrine Disruptors, Endocrine Society, Washington, DC, June 9th, 2009.
140. "The Quandary of Environmental Contaminants in Human Milk", 25th Anniversary of US Surgeon General's Report on Breastfeeding, Washington, DC, June 13th, 2009.
141. "Linking Exposures to Environmental Toxicants with Learning Problems and Psychopathology in Children." Northwest Conference on Children's Health and Environment, Tukwila, Washington, October 1st, 2009.
142. "The Second Coming of the Sanitarians", Pediatric Grand Rounds, University of California at Davis Children's Hospital, Sacramento, California, October 9th, 2009.
143. "The Second Coming of the Sanitarians", National Institute of Public Health, Rennes, France, November 4th, 2009.
144. "Linking Exposure to Environmental Toxicants with ADHD in Children." Symposium on ADHD. Riyadh, Saudi Arabia, November 7th, 2009.
145. "The Interplay of Genetic and Environmental Influences in Common Conditions of Children." Macquarie University, Department of Geology, Sydney, Australia, November 18th, 2009.
146. "The Lingering Legacy of Lead Toxicity: A Call for the Global Elimination of Lead Exposure." Pacific Basin Consortium Symposium on Environment and Health, Perth, Australia, November 13th, 2009.
147. "The Second Coming of the Sanitarians", SFU President's Lecture, Simon Fraser University, Burnaby, BC, March 4th, 2010.
148. Third Annual Controversies in Pediatric Environmental Health Debate, "Should the American Academy of Pediatrics Sponsor a Ratings Board to Provide Evidence-based Ratings for Media?" A debate by James Sargent and Donald Shifrin (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Vancouver, BC, May 2nd, 2010.
149. "Efficacy of Reducing Lead Hazards in Housing on Lead-Contaminated House Dust, Blood Lead Concentration and Intellectual Abilities in Children." Pediatric Academic Societies Meeting, Vancouver, BC May 1st, 2010.
150. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson." Pediatric Grand Rounds, Cornell Weill Medical College, New York, New York. May 25th, 2010.
151. "Excavating the Enigmas of Childhood Lead Toxicity", Guest Lecturer, "Introduction to Toxicology, Harvard School of Public Health, Boston, Massachusetts, October 27th, 2010.

152. "The Conquest of Lead Poisoning: A Pyrrhic Victory", Lead Action Collaborative, New England Carpenters Center, Boston, Massachusetts, October 28th, 2010.
153. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson." Academy of Breastfeeding Medicine, San Francisco, California, October 29th, 2010.
154. "Bisphenol A and Behavior Problems in Children". Eastern Perinatal Conference, Kingston, Ontario, November 10th, 2010.
155. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" UBC Statistics Department Seminar, November 18th, 2010.
156. "Protecting Children from Environmental Toxicants." Children's Hospital of Quebec, University of Laval, Quebec City, Quebec, December 17th, 2010.
157. "Low-level Toxicity: Implications for Research and Policy", Joint Talks by C. Arden Pope and Bruce Lanphear, SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA January 7h, 2011.
158. "Crime of the Century: Lead Toxicity in the 20th Century", Panel Presentation and Discussion, UC Davis, Sacramento, California April 7th, 2011.
159. Fourth Annual Controversies in Pediatric Environmental Health Debate, "Should Parent Slather their Children with Sunscreen?" A debate with Russell Chesney, MD and Sophie Balk, MD, (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Denver, Colorado, May 1st, 2011.
160. The Conquest of Lead Toxicity: A Pyrrhic Victory", Canadian Water Network, Ecole Polytechnique de Montreal, Montreal, Canada, June 9h, 2011.
161. The Contribution of Environmental Influences on Chronic Disease, Canadian Partnership for Health and Environment, Toronto, Canada, June 16th, 2011.
162. "The Second Coming of the Sanitarians", Environmental and Occupational Health Seminar, University of Washington School of Public Health, Seattle, WA, May 12th, 2011.
163. "Crime of the Century: The Failure to Prevent the Lead Pandemic". Sterling Prize in Controversy, Wosk Centre, Simon Fraser University, Vancouver, BC, October 19th, 2011.
164. "Measuring Exposure: The Benefits and Limits of Biomarkers". Canadian Institute for Human Development, Child and Youth Research, Montreal, Canada, December 6th, 2011.
165. "Rachel Carson: Clarity of Vision". SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA, January 6th, 2012.
166. "The Truth About Toxins: What Parents and Health Professionals Should Know". Environmental Influences on Neurodevelopment: Translating the Emerging Science into Public Health Policy". UCLA School of Public Health, Los Angeles, California, January 12h, 2012.

167. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". Mattel Children's Hospital, Los Angeles, California, January 13th, 2012.
168. "Why Should We Share Data?", Data Sharing Strategies for Environmental Health Workshop, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, February 6th and 7th, 2012.
169. "The Science and Prevention of Lead Toxicity" (Keynote Presentation), Forum on Lead Toxicity: A Little is Still Too Much", Macquarie University, Sydney, Australia, June 5th, 2012
170. "Canada Environmental Health Atlas Knowledge Translation Workshop", Canadian Public Health Association, Edmonton, Alberta, June 13th, 2012.
171. "First Annual Controversies in Pediatric Environmental Health Debate: Should organophosphate pesticides be reduced or banned?" A debate with Brenda Eskenazi and Bruce Lanphear (Rob McConnell, Moderator). International Society for Environmental Epidemiology, Columbia, SC, August 28th, 2012.
172. "Supralinear Dose-Response Relationship of Environmental Toxicants: Research and Policy Implications." Moderator and Speaker, with Arden Pope, Roel Vermeulen and Bruce Lanphear. International Society for Environmental Epidemiology, Columbia, SC, August 29th, 2012.
173. Tanya Froehlich and Bruce Lanphear, "ADHD and Environmental Toxicants: Time for Prevention?", Society for Development and Behavioral Pediatrics, Phoenix, AZ, September 9th, 2012.
174. "The Epidemic of Childhood Disabilities: A Failure to Regulate". Workshop on Children's Rights and Corporate Responsibility, Green College, University of British Columbia, Vancouver, BC, October 19th, 2012.
175. "Low-level Toxicity: Much Ado About Nothing?", Department of Preventive Medicine Seminar, University of Southern , California, Los Angeles, California, October 23rd, 2012.
176. "Reflections on Silent Spring". (Invited Keynote). International Society for Exposure Sciences, Seattle, Washington, October 28th, 2012.
177. "Randomized Controlled Trials in Children's Environmental Health: Underutilized or Unethical?" The University of Washington Northwest Pediatric Environmental Health Specialty Unit and Center for Child Environmental Health, Seattle, Washington, February 26th, 2013.
178. "Crime of the Century: Our Failure to Prevent the Lead Pandemic". Dali Lana School of Public Health and of School Environment, University of Toronto, Toronto, Ontario, March 26th, 2013.
179. "The Ongoing Search for a Threshold". International Conference of Toxicology, Seoul, Korea, July 1, 2013.

180. "Blood Lead Concentrations and Cardiovascular Mortality in the United States: The NHANES Mortality Follow-up Cohort Study". International Society for Environmental Epidemiology, Basel, Switzerland, August 2, 2013.
181. "The Conquest of Lead Poisoning: A Pyrrhic Victory". Corporations and Global Health Governance. Simon Fraser University, Burnaby, British Columbia. September 17 h, 2013.
182. "Striking at the Root: Changing the Narrative on the Causes of Disease". Corporations and Global Health Governance. Simon Fraser University, Burnaby, British Columbia. September 17th, 2013.
183. "Crime of the Century: The Failure to Prevent the Lead Pandemic". Pacific Basin Consortium, East-West Center, Honolulu, Hawaii. September 26, 2013.
184. "Low-level Toxicity: Policy Implications for the 21st Century". Symposium on Policy Implications of Environmental Exposures in the 21st Century. Pacific Basin Consortium, East-West Center, Honolulu, Hawaii. September 27, 2013.
185. "Excavating the Enigmas of Childhood Lead Toxicity". Network for Soil Contamination Research (INSCR), Delhi University, New Delhi, India. October 22nd, 2013.
186. "The Lingering Legacy of Lead Toxicity: A Call for the Global Elimination of Lead Exposure", World Health Organization, New Delhi, India. October 24th, 2013. "The Environmental Health Atlas: A Portal to Discover the Promises of Environmental Health." National Institute of Environmental Health Sciences, Raleigh-Durham, NC, November 10th, 2013.
187. "Protecting Children from Environmental Toxins". Japan Dioxin and Endocrine Disruptors Preventive Action, Tokyo, Japan, November 24 h, 2013.
188. "ADHD: A Preventable Epidemic?" Alberta Children's Hospital, Calgary, Alberta, December 16th, 2013.
189. "Little Things Matter: The Impact of Toxins on the Developing Brain". Early Years Conference, Vancouver, British Columbia, January 30th, 2014.
190. "Little Things Matter: The Impact of Toxins on the Developing Brain". Dalhousie University, Halifax, Nova Scotia, March 6 h, 2014.
191. "Low-level Toxicity of Environmental Toxins: Much Ado About Nothing?". Dalhousie University, Halifax, Nova Scotia, March 6th, 2014.
192. "The Canadian Environmental Health Atlas: A Portal to Discover the Promises of Environmental Health." School of Occupational and Environmental Health, University of British Columbia, March 28th, 2014.
193. "Little Things Matter: The Impact of Toxins on the Developing Brain". British Columbia Healthy Child Alliance, Vancouver, British Columbia, April 2nd, 2014.

194. "Sixth Annual Controversies in Pediatric Environmental Health Debate, E-Cigarettes: A weapon in the war against tobacco or a threat to tobacco control. (Moderator). Featuring Greg Connelly and James Sargent. Pediatric Academic Societies, Vancouver, May 4th, 2014.
195. "Striking at the Root Causes of Chronic Disease in Children" (Moderator). James Sargent, Joel Bakan and David Kessler, May 5th, 2014.
196. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). OHKA Healthy Homes Alliance, Omaha, Nebraska, May 15th, 2014.
197. "Excavating environmental risk factors for autism: Suspects and strategies". A workshop on examining a multi-systems approach to autism and the environment: challenges and opportunities for research". Toronto, Ontario, June 23rd-24th, 2014.
198. "Lead Poisoning: Tackling a Global Problem" (Co-Moderator and Speaker). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
199. "Interventions to Reduce Exposures to Environmental Hazards in Pregnant Women and Children", (Moderator and Speaker). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
200. 3rd Annual ISCHE-Sponsored Debate: Should there be any restrictions on universities or academicians receiving payment from industry or other sources? (Moderator). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
201. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, September 5th, 2014.
202. "Environment Matters", Children's Environmental Health Panel. Society for Environmental Journalists, New Orleans, Louisiana, September 6th, 2014.
203. "Insidious Influence of Industry on Science: How Corporations Undermine Science", 5th Annual C. Everett Koop Distinguished Lecture, "Corporate Threats to Children's Health", with Joel Bakan and James Sargent, Dartmouth University, New Hampshire, October 6th, 2014.
204. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", John Rosen Memorial Lecture, Montefiore Medical Center, New York, New York, October 8th, 2014.
205. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). Prenatal Environmental Health Education (PEHE) Conference, University of Ottawa. Ottawa, Ontario, November 21st, 2014.
206. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). ISEE Asian Regional Meeting, Shanghai, China, November 30th, 2014.
207. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", John Rosen Memorial Lecture, ISEE Asian Regional Meeting, Shanghai, China, November 31st, 2014.

208. ”Data Visualization”, with Joe Braun and Allan Just, Pediatric Environmental Health Scholars Retreat, Reston, VA, December 6th, 2014.
209. “Victories in Public Health: Progress or Adaptation?” SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA January 8th, 2015.
210. “Food in the Industrial Era: Is Backward the Way Forward?” Children’s Environmental Health Network, Austin, Texas, February 4th, 2015.
211. “Excavating the enigmas of childhood lead toxicity”. Broken Hill City Council and Lead Reference Group, Broken Hill, New South Wales, Australia, March 3rd, 2015.
212. “Prevention Paradox: Why a Little Lead is Too Much”. Unequal Exposure Symposium, Climate Change Research Center, University of New South Wales, March 5th, 2015, Sydney, Australia.
213. “Crime of the Century: Our Failure to Prevent the Lead Pandemic”. 10th Annual Break the Cycle Conference, Emory University, Atlanta, Georgia. April 23rd, 2015.
214. “The Staggering Cost of Lead Toxicity and the Unbelievable Benefit of Preventing It”. 10th Annual Break the Cycle Conference, Emory University, Atlanta, Georgia. April 24th, 2015.
215. Seventh Annual Controversies in Pediatric Environmental Health Debate, “GMOs: A Hazard or Harvest of Health?” A debate with Joel Forman, MD and Daniel Goldstein, MD, (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, San Diego, California, April 27th, 2015.
216. “Impact of Dwellings on Child Health”, Canadian Green Building Council Conference, Vancouver Convention Center, Vancouver, BC, April 28. 2015.
217. “Impact of Tobacco on the Developing Brain”, Developmental Effects of Nicotine and Implications for Emerging Tobacco Products, Rockville, Maryland, May 5th, 2015.
218. “Impact of Toxins on the Developing Brain” India Tour (Bengaluru, Trivandrum, Kolkata, and Chandigarh) Sponsored by PAN-India, September 4th-11th, 2015.
219. “Impact of Dwellings on Child Health”, Green School Summit, Calgary, Alberta, September 25th. 2015.
220. “Prevention Paradox: Why a Little Lead is Too Much”, A debate with George Rhoads, Montefiore Medical Center, Tarrytown, October 2nd, 2015.
221. “Crime of the Century: Our Failure to Prevent the Lead Pandemic” (Keynote Presentation), University of Cincinnati Department of Environmental Health 50th Anniversary Gala, Cincinnati, Ohio, October 9th, 2015.
222. “Impact of Toxins on the Developing Brain” (Keynote Presentation) Children’s Environmental Health Centers Annual Meeting, Washington, DC, October 31, 2015.

223. "The Impact of Toxins on the Developing Brain: Our Failure to Prevent Brain-based Disorders in Children", National Core for Neuroethics, UBC November 12th, 2015.

Grants

Active Grant Awards

1. Co-Investigator (Kieran Phelan, PI). "Injury Prevention in a Home Visitation Population". NICHD, 09/28/10 to 07/31/16, $2,000,000 (total direct costs over 5 years) (10% effort).
2. Principal Investigator (Multiple PI Award with Aimin Chen and Kimberly Yolton). "Longitudinal study of exposures to PBDEs and PFCs and child behavior". NIEHS, 10/01/11 to 09/30/16, $2,150,000 (total direct costs over 5 years) (20% effort).
3. Principal Investigator. Knowledge translation tools for capacity building for an online Canadian Environmental Health Atlas. 03/01/12 to 02/28/13, Canadian Institutes of Health Research, $98,974 (10% effort).
4. Co-investigator (Joseph Braun, PI) Endocrine Disrupting Chemicals, Thyroid Hormones and Child Neurobehavior. 06/01/2015-03/31/2019. National Institutes of Health, $469,251 (5% effort). The purpose of this study is test if and when early life exposures to phthalates, triclosan, or bisphenol A adversely impacts children's cognition and behavior.
5. Principal Investigator (with Lawrence McCandless). Approaches to examine the impact of complex chemical mixtures on fetal growth using the HOME Study. 07/01/2015-06/30/2016. CIHR, $12,000 (5% effort).
6. Principal Investigator, Canadian Environmental Health Atlas Knowledge Translation to produce videos and interactive tools. 06/01/2015-0/30/2016. Canadian Internet Registration Authority, $50,000 (10% effort).
7. Consultant (Joseph Braun, PI) Early Life Perfluoroalkyl Substance Exposure and Obesity: Mechanisms and Phenotyping. 02/01/2016-03/31/2021. National Institutes of Health, $469,251 (5% effort). The purpose of this award is to study the impact of exposure to perfluoroalkyl chemicals on the development of child obesity, adverse cardiometabolic markers and gene regulation.

Past Grant Awards

1. Principal Investigator, "Dust-Lead and Blood Lead Levels among Urban Children". The National Center for Lead-Safe Housing, $561,619, 06/15/93 to 08/31/94. Department of Housing and Urban Development Contract MDLPT0001-93. (25% effort).
2. Principal Investigator, "Determinants of Lead Exposure among Children in Monroe County, NY", NIEHS Pilot Grant, University of Rochester School of Medicine and Dentistry, Department of Environmental Medicine. $7,600, 06/15/93 to 12/31/95. (0% effort)
3. Principal Investigator, "The Effectiveness of Dust Control in Reducing Children's Blood Lead Levels" U.S. Department of Housing and Urban Development, $128,394, 04/01/94 to 05/30/95. (25% effort).
4. Principal Investigator, "Primary Prevention of Exposure to Lead". Centers for Disease Control and Prevention, $832,228, 09/30/94 to 10/01/98. (25% effort)
5. Principal Investigator, "Lead-Contaminated House Dust and Children's Blood Lead Levels". National Center for Lead-Safe Housing, $43,260, 10/01/96 to 03/30/96. (25% effort).
6. Co-investigator (Christy, PI), “Tuberculosis Screening in Children”. New York Department of Health, $15,000, 01/01/95 to 12/31/96. (0% effort)
7. Co-investigator (Weitzman, PI), “Fellowship Training in General Pediatrics” (Grant # D28PE50008). Bureau of Health Professions, HRSA, U.S. Public Health Service, $1,752,816, 06/01/96 to 05/30/97. (10% effort).
8. Principal Investigator, “Neurobehavioral Effects of Low-Level Childhood Lead Exposure”. University of Rochester School of Medicine & Dentistry, $8,560, 06/01/96 to 05/30/97. (0% effort)
9. Principal Investigator, “Neurobehavioral Effects of low-level Lead Exposure in Children”. NIEHS Pilot Grant, University of Rochester Department of Environmental Medicine, $20,035, 09/01/97 to 08/30/97. (0% effort).
10. Co-investigator (Howard, PI), “Effect on Breastfeeding of Pacifiers and Bottle Feeding”. Bureau of Maternal and Child Health, $420,333, 10/01/96 to 09/30/00. (2.5% effort)
11. Co-investigator (Canfield, PI) “Lead and Children’s Cognitive Functioning”, Research Grants Program, Cornell University. $17,000, 10/01/96 to 09/31/97 (0% effort).
12. Principal Investigator, “Neurobehavioral Effects of Low-Level Lead Exposure in Children” (RO1-ES 08338). National Institute of Environmental Health Sciences, 12/01/96 to 11/31/01, $1,946,848. (25% effort).

13. Co-investigator, (Aligne, PI). "Reduction in Passive Smoking among Children with Asthma: A Randomized Trial of HEPA Air Filtration." 10/01/96 to 09/31/97, $6,000. KIDD Grant, Rochester General Hospital (0% effort).
14. Co-investigator, (DeWitt, PI). "Faculty Development in General Pediatrics". Bureau of Health Professions, Health, Department of Health and Human Services 07/01/97 to 06/30/00, $338,000. (15% effort).
15. Principal Investigator, "A Side-by-Side Comparison of Allergen Sampling Methods", U.S. Department of Housing and Urban Development, 01/02/98 to 12/31/98, $163,065. (15% effort).
16. Principal Investigator, "National Research Service Award - Fellowship Training in General Pediatrics and Adolescent Medicine" (1T32PE10027), Health Resources and Services Administration, DHHS. 07/01/98 to 06/30/03. $634,408. (0% effort).
17. Co-investigator, (Steiner, PI) "Survey of Directors and Graduates of NRSA Fellowship Training Programs", Health Resources and Services Administration, Department of Health and Human Services. 06/01/98 to 06/30/99.
18. Principal Investigator, "Effect of Soil Remediation on Children's Blood Lead Levels in Midvale, Utah". U.S. Environmental Protection Agency, 08/01/98 to 07/30/99. $62,550. (15% effort).
19. Co-investigator, (Phelan, PI) Trends and Patterns in Playground Injuries among U.S. Children." Ambulatory Pediatric Association, 05/05/99 to 05/04/00. $9,000 (0% effort).
20. Principal Investigator, "Risk Assessment for Residential Lead Hazards". U.S. Department of Housing and Urban Development, 09/01/99 to 08/30/00. $102,435. (25% effort).
21. Principal Investigator, "Residential Exposures associated with Asthma in U.S. Children and Adolescents" U.S. Department of Housing and Urban Development, 07/16/99 to 03/15/00. $30,400. (20% effort).
22. Principal Investigator, "Effectiveness of Lead Hazard Control Interventions – A Systematic Review" National Center for Lead-Safe Housing, 10/01/99 to 06/01/00. $22,500 (10% effort).
23. Principal Investigator, "Racial Disparity in Blood Lead Levels due to Genetic Variation in Calcium Absorption". NIEHS Pilot Grant, Center for Environmental Genetics, University of Cincinnati, 04/01/00 to 03/31/01. $28,130 (0% effort).
24. Principal Investigator, "International Pooled Analysis of Prospective, Lead-Exposed Cohorts". National Institute of Environmental Health Sciences, National Institutes of Health, 08/15/00 to 09/14/01, $16,000. (2.5% effort).
25. Principal Investigator, "A Randomized Trial to Reduce ETS in Children with Asthma" (RO1-HL/ES65731). National Heart, Lung and Blood Institute, National Institutes of Health, 09/29/00 to 09/28/04, $1,546,848. (25% effort).

26. Co-investigator, (Geraghty, PI) “Breastfeeding Practices of Mothers of Multiples”. Ambulatory Pediatric Association, 05/01/01 to 04/30/02. $5,000 (0% effort).
27. Principal Investigator (Subcontract), “A Longitudinal Study of Lead Exposure and Dental Caries”. National Institute of Dental and Craniofacial Research, National Institutes of Health, 08/01/01 to 07/30/04. $300,000 (10% effort).
28. Co-investigator (Phelan, PI), “Fatal and Non-Fatal Residential Injuries in U.S. Children and Adolescents” U.S. Department of Housing and Urban Development, 03/01/01 to 11/31/01. $40,700. (5% effort).
29. Principal Investigator, “Prevalent Neurotoxicants in Children” (PO1-ES11261). National Institute for Environmental Health Sciences and U.S. Environmental Protection Agency, 09/01/01 to 09/31/06, $5,000,000. (30% effort).
30. Principal Investigator, “International Pooled Analysis of Lead-Exposed Cohorts”. Centers for Disease Control (RO1/CCR 521049). Centers for Disease Control, 09/15/01 to 09/14/02, $28,473. (3% effort).
31. Principal Investigator, supplement to “Prevalent Neurotoxicants in Children” (PO1-ES11261). NIEHS, 09/01/02 to 09/31/07, $1,800,000. (10% effort).
32. Co-Investigator, “ADHD Phenotype Network: Animal Model to Clinical Trial”. National Institute of Neurologic Diseases, 09/15/02 to 06/30/05 (15% effort).
33. Principal Investigator, “Linkage of ADHD and Lead Exposure”, Springfield, Ohio Department of Health, 02/01/03 to 06/01/04, $25,000. (0% effort).
34. Co-investigator (Yolton, PI) “Explorations of ETS Exposure on Child Behavior and Sleep” NIEHS, 04/01/04 to 03/30/06, $300,000. (5% effort).
35. Co-investigator (Haynes, PI) “MRI as a Biomarker of Manganese Exposure”. NIEHS, 09/01/04 to 08/30/06, $300,000. (5% effort).
36. Co-investigator (National Center for Healthy Housing, PI) “Development of a Standardized Housing Assessment for Asthma”, U.S. Department of Housing and Urban Development, 11/01/05 to10/31/07, $50,000. (5% effort).
37. Co-Investigator (Hershey, PI) “Epithelial Genes in Allergic Inflammation” National Institutes of Allergy and Infectious Diseases”, 07/01/06 to 06/30/07, $4,787.541. (3% effort).
38. Co-Investigator and Mentor (Wilson, PI), “Racial Difference in DNA Adducts in Tobacco-Exposed Children”. Dean’s Scholar Award, University of Cincinnati, 02/22/06 to 01/21/09, $150,000 (5% effort).

39. Principal Investigator, "National Research Service Award - Fellowship Training in Primary Care Research," (1T32PE10027), Health Resources and Services Administration, DHHS. 07/01/98 to 06/30/08. $1,600,000. (0% effort).
40. Co-Investigator and Mentor (Kahn, PI). "Childhood Asthma in an Era of Genomics: Will the Generalist's Role be Recast?" Robert Wood Johnson Generalist Physician Faculty Scholars Program" 06/01/04 to 05/30/08, $300,000.
41. Co-Investigator and Mentor (Spanier, PI), "Exhaled Nitric Oxide to Manage Childhood Asthma". National Heart, Lung and Blood Institute, 07/01/06 to 06/31/08, $200,000 (10% effort).
42. Co-investigator (Sub-Contract PI), BYPL Vanguard Center (Specker, Principal Investigator), "National Children's Study", National Institute for Child Health and Development, 11/01/05 to 10/31/10, $500,000. (20% effort). [Relinquished with relocation to SFU].
43. Associate Director and Co-Investigator, (Ho, PI). "Center for Environmental Genetics," NIEHS, 04/01/08 to 3/31/13, $1,000,000 (10% effort). [Relinquished with relocation to SFU.]
44. Co-Investigator (Yolton, PI). "Tobacco Smoke and Early Human Behavior". Clinical Innovator Award, Flight Attendant Medical Research Institute", 07/01/07 to 06/30/10, $300,000. (3% effort).
45. Co-Investigator (Spanier, PI). "Low Level Prenatal Tobacco Exposure and Infant Wheeze." Young Clinical Scientist Award, Flight Attendant Medical Research Institute, 07/01/07 to 06/30/12, $300,000. (5% effort).
46. Co-Investigator and Mentor (Spanier, PI). K23, "Prenatal Low Level Tobacco & Phthalate Exposure and Childhood Respiratory Health". National Institute for Environmental Health Sciences, 12/1/07 to 11/30/12, $623,679 (0% funded effort).
47. Co-investigator (Yolton, PI). "Neurobehavioral effects of insecticide exposure in pregnancy and early childhood." NIEHS, 09/01/09 to 08/31/12.
48. Principal Investigator (Bruce Lanphear, PI), "A Community-Based Trial to Prevent Lead Poisoning and Injuries," National Institute for Environmental Health Sciences, 04/01/07 to 03/30/13, $2,000,000. (25% effort).
49. Co-Investigator (Kim N. Dietrich, PI). "Early Lead Exposure, ADHD & Persistent Criminality: Role of Genes & Environment," National Institute for Environmental Health Sciences, 04/01/07 to 3/31/2013, $1,250,000. (2.5% funded effort).
50. Co-Investigator and Sub-Contract PI (Brenda Eskenazi, PI). This supplemental award was to conduct a pooled analysis of prenatal organophophate pesticide exposures with birth outcomes and neurodevelopment in children using 4 US birth cohorts. NIEHS, 09/01/2009 to 08/31/2013, $96,000 (0% effort).

51. Mentor and Supervisor (Glenys Webster, PI). Michael Smith Foundation for Health Research Postdoctoral Training Award, 03/01/12 to 02/28/15, $134,500 (5% effort).
52. Co-Principal Investigator (Tye Arbuckle, PI). Maternal-Infant Research on Environmental Chemicals: Effects on Child Development (MIREC-CD). 06/26/11 to /5/25/14, Health Canada Chemical Management Program, $283,000 (10% effort).
53. Co-Investigator (Patti Dods and Amanda Wheeler, co-PIs). Phthalate Exposure and the development of asthma in the CHILD Study. 06/01/11 to 05/30/14, Health Canada Chemical Management Program, $204,000 (5% effort). Consultant (Stephanie Engel, PI). A pooled investigation of prenatal phthalate exposure and childhood obesity. 11/01/2012 – 10/31/15, NIEHS. $275,000. (5% effort).
54. Co-Investigator (Ryan Allen, PI). A randomized air filter intervention study of air pollution and fetal growth in a highly polluted community. 06/08/2012 – 05/30/15, CIHR $348,000 (10% effort).
55. Co-Investigator (William Fraser and Tye Arbuckle, co-PIs). MIREC-CD Biomonitoring Study in Vancouver. 09/01/2013 – 08/30/2014. Health Canada, $120,138 (10% effort).

Ethics Training for Research

CITI (Collaborative Institutional Training Initiative) (Reference# 7159023). Academic and Regional Health Centers Curriculum Course, completed on December 16th, 2011.

CITI (Collaborative Institutional Training Initiative) (Reference# 7160515), Canada GCP Curriculum Course, completed on December 16th, 2011.

CITI (Collaborative Institutional Training Initiative) (Reference# 8316270), Human Subjects Core Curriculum, completed on August 17h, 2012.

CITI (Collaborative Institutional Training Initiative) (Reference# 13561457), Academic and Regional Health Centers Core Curriculum, completed on September 1st, 2014.

CITI (Collaborative Institutional Training Initiative) (Reference# 16954900), Human Subjects Research Core Curriculum, completed on October 31st, 2015.

EXHIBIT 2

Review

Lead Exposures in U.S. Children, 2008: Implications for Prevention

Ronnie Levin,[1] Mary Jean Brown,[2] Michael E. Kashtock,[3] David E. Jacobs,[4] Elizabeth A. Whelan,[5] Joanne Rodman,[6] Michael R. Schock,[7] Alma Padilla,[1] and Thomas Sinks[2]*

[1]U.S. Environmental Protection Agency, Boston, Massachusetts, USA; [2]Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [3]Food and Drug Administration, Washington, DC, USA; [4]Department of Housing and Urban Development, Washington, DC, USA; [5]National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA; [6]U.S. Environmental Protection Agency, Washington, DC, USA; [7]U.S. Environmental Protection Agency, Cincinnati, Ohio, USA

Objective: We reviewed the sources of lead in the environments of U.S. children, contributions to children's blood lead levels, source elimination and control efforts, and existing federal authorities. Our context is the U.S. public health goal to eliminate pediatric elevated blood lead levels (EBLs) by 2010.

Data sources: National, state, and local exposure assessments over the past half century have identified risk factors for EBLs among U.S. children, including age, race, income, age and location of housing, parental occupation, and season.

Data extraction and synthesis: Recent national policies have greatly reduced lead exposure among U.S. children, but even very low exposure levels compromise children's later intellectual development and lifetime achievement. No threshold for these effects has been demonstrated. Although lead paint and dust may still account for up to 70% of EBLs in U.S. children, the U.S. Centers for Disease Control and Prevention estimates that ≥ 30% of current EBLs do not have an immediate lead paint source, and numerous studies indicate that lead exposures result from multiple sources. EBLs and even deaths have been associated with inadequately controlled sources including ethnic remedies and goods, consumer products, and food-related items such as ceramics. Lead in public drinking water and in older urban centers remain exposure sources in many areas.

Conclusions: Achieving the 2010 goal requires maintaining current efforts, especially programs addressing lead paint, while developing interventions that prevent exposure before children are poisoned. It also requires active collaboration across all levels of government to identify and control all potential sources of lead exposure, as well as primary prevention.

Key words: children's health, environmental health, lead poisoning, primary prevention. *Environ Health Perspect* 116:1285–1293 (2008). doi:10.1289/ehp.11241 available via *http://dx.doi.org/* [Online 19 May 2008]

Some recent tragedies have evinced a more complicated risk pattern for pediatric lead exposures in the United States than had previously been considered:

- 21 April 2000, New Hampshire: A 2-year-old Sudanese refugee died from exposure to lead paint, the first U.S. child known to die from lead poisoning in 10 years [Centers for Disease Control and Prevention (CDC) 2005a].
- July 2002, New York City: A 1-year-old's elevated blood lead level was traced to ceramic dinnerware without visible signs of wear (CDC 2004a).
- 23 July 2003, Massachusetts: A lead-coated copper wall and roof were identified in a child's condominium where dust lead levels were 224,377 μg/ft^2 (Brown MJ, unpublished memo to the Consumer Product Safety Commission, 2004).
- 2004, Oregon: A child was hospitalized after ingesting a necklace made with lead, resulting in voluntary recall of 150 million pieces of children's jewelry (CDC 2004b).
- 23 March 2006: Minnesota: A 4-year-old died from lead poisoning after swallowing a charm with 99% lead content received with a purchase of shoes (CDC 2006).

The implications of these and similar events drove members of core federal agencies to jointly construct a more complete picture of potential lead exposures than had previously been compiled.

Introduction

Lead is corrosion-resistant, dense, ductile, and malleable and has been used since at least 3500 BCE. Atmospheric lead levels increased more than six orders of magnitude over the past six millennia accompanying population and economic growth (Figure 1) (Davidson and Rabinowitz 1992). Blood lead levels (BLLs) of U.S. children rose sharply between 1900 and 1975 as increased lead emissions caused widespread contamination. Changes in federal laws have reversed this trend, including eliminating leaded gasoline from on-road vehicles, banning the sale of leaded house paint, and prohibiting lead solder in public water systems, plumbing components, and food and drink cans. The sharp reduction in children's BLLs between 1976 and 1989 demonstrates that these policies have been effective (Mahaffey et al. 1982; Pirkle et al. 1998). However, children continue to be exposed to lead. In 1999–2002, an estimated 310,000 (1.6%) U.S. children had BLLs ≥ 10 μg/dL, and 1.4 million had BLLs of 5–9 μg/dL (almost 14%) (CDC 2005b).

The adverse health effects of lead—including death, insanity, nervous system damage, and sterility—have been reported since the second century BCE (Major 1945). Even low lead exposure affects children's intellectual development and lifetime achievement. Since the 1980s, studies have linked BLLs < 10 μg/dL in children 1–5 years of age with decreased IQ and cognition, with demonstrated effects evident at about 2 μg/dL (Jusko et al. 2008). No threshold for effects has been demonstrated.

In 2000, the United States adopted the goal of reducing all exposures to lead and eliminating elevated blood lead levels (EBLs; BLLs ≥ 10 μg/dL) in children by 2010 (Department of Health and Human Services 2000). However, projections of future decreases in the number of children with EBLs (Jacobs et al. 2002) assume a funding schedule that is not fully actualized. The nation's goal to eliminate childhood BLLs > 25 μg/dL by 2000 was not met (Jacobs and Nevin 2006). The 2010 goal may fall short without augmented investment.

Screening children for lead and abating lead paint hazards in homes of children with EBLs must continue. But given ubiquitous lead contamination, merely reducing hazards in residences of children identified with EBLs will not suffice. Childhood lead poisoning prevention programs (CLPPPs) must consider current and past uses of lead as well as behaviors that leave specific populations vulnerable to excessive lead exposures. To be effective, CLPPPs must shift to primary prevention.

Sources of Lead Exposure

Deteriorating lead paint and contaminated dust and soil are the primary, but not the only, causes of EBLs among U.S. children. Lead is used in thousands of applications, all of which constitute potential exposure sources [U.S. Environmental Protection Agency

Address correspondence to R. Levin, U.S. EPA SEP, One Congress St., Boston MA 02114 USA. Telephone: (617) 918-1716. Fax: (617) 918-0716. E-mail: levin.ronnie@epa.gov

*Current address: National Center for Healthy Housing, Columbia, Maryland, USA.

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(EPA) 2006a]. Recent data indicate that ≥ 30% of children with EBLs do not have an immediate lead paint hazard. For example, in 2004 in Arizona, soil was the most common identified proximate exposure source, accounting for about 24% of pediatric EBL cases, followed by paint (17%), folk remedies and pottery (17%), dust (15%), and miscellaneous other sources (19%). In 8% of cases, no lead source was identified (Arizona Department of Health Services 2005).

Nonpaint lead exposure sources are insufficiently characterized, and their importance is often underestimated. When a child with an EBL is reported, investigators look for lead paint in places where s/he spends time, exploring alternative lead exposure sources only when no paint hazards are found. Thus, for some children, significant nonpaint sources may be missed. Evidence also suggests that for children with BLLs < 10 µg/dL, no single exposure source predominates (Bernard and McGeehin 2003).

Lead in the environment. The United States is the third largest lead producer, producing about 450,000 tons in 2003 (U.S. Geological Service 2004). In 2003, the United States consumed about 1.5 million tons of lead (Commodity Research Bureau 2006). Facilities using lead can raise exposures for adjacent populations. Not all sources are obvious, and many users are exempt from reporting. In Massachusetts in 2003, for instance, 252 facilities used nearly 9.3 million pounds of lead, with the largest releases reported by municipal waste combustors (Table 1).

Air. During the 20th century, leaded gasoline was the predominant source of airborne lead. Today, industrial emissions predominate. In 2001, the U.S. Environmental Protection Agency (EPA) reported that industrial emissions accounted for 78% of air lead, fuel consumption accounted for 10%, and the transportation sector accounted for 12% (U.S. EPA 2007a). In 2004, four waste treatment plants were among the 20 largest dischargers of lead submitting data to the Toxics Release Inventory (TRI) of the U.S. EPA (U.S. EPA 2007d).

After declining for > 25 years, U.S. air lead levels rose in 2004–2006 (Figure 2) (U.S. EPA 2007a). The highest air concentrations of lead are found near smelters and battery manufacturers. At present, these are the only violations of the national air lead standards (U.S. EPA 2007a). However, national air lead emission data cannot accurately portray local lead emissions or their risk for proximate populations. Exposure modeling at the U.S. EPA indicates that for the 20 highest air emitters, local emissions are significantly related to local BLLs (U.S. EPA 2007b).

Not all sources of lead are listed in the U.S. EPA TRI. Municipal incinerators, small operations such as auto repair shops, off-road vehicles including NASCAR, and propeller aircraft using aviation gasoline (avgas) are exempt from reporting, fall below reporting quantities, or choose not to report; nonetheless, they can contaminate surrounding communities. For example, at one airport where many airplanes used avgas, average and maximum air lead levels were 0.030 and 0.302 µg/m^3, respectively, versus background levels of 0.007 and 0.018 µg/m^3 (Environment Canada 2000). Another study showed that even at an airport with few planes using avgas, air lead levels were higher downwind than upwind (Illinois Environmental Protection Agency 2002).

Demolition of old buildings contributes to local air lead levels and can increase BLLs in children (Farfel et al 2003; Rabito et al 2007).

Soil. Lead binds tightly to soils, and eight decades of leaded gasoline combustion and past industrial emissions have left a legacy entrained in soil. Peeling lead paint on residences also contaminates soil, especially in distressed neighborhoods. Because of higher traffic levels and denser housing, the soil in urban areas can average 800–1,200 µg/g (Duggan and Inskip 1985; Lanphear 1998a). Soil from play areas has a larger impact on children's BLLs than soil from other areas (Lanphear et al. 1998b; Mielke and Reagan 1998). Lead tire weights that fall off are quickly abraded and ground into tiny pieces by traffic, resulting in high dust-loading rates, especially in urban areas (Root 2000). Lead exposure also occurs through produce grown in contaminated soil (Finster et al. 2004).

Children living near mining and smelting sites are at risk for EBLs (Maisonet et al. 1997; Murgueytio et al. 1996; Swarup et al. 2005). Studies find effects even 20 years after smelter closing (Diaz-Barriga et al. 1997).

Historical research to uncover past commercial activities can identify current sources of exposure (Eckel et al. 2001). For instance, a Washington State study (Wolz et al. 2003) found that homes near locations where lead arsenate was used as a pesticide between 1905 and 1947 had significantly higher soil and indoor dust levels.

Elevated soil lead levels are found at more than two thirds of Superfund sites in all 50 states [Agency for Toxic Substances and Disease Registry (ATSDR) 2005]. Lead is the chemical most frequently released from uncontrolled hazardous waste sites; in 1997, the ATSDR identified lead contamination in 59% of the sites monitored (ATSDR 2005). Numerous historical mining and smelting districts are now Superfund sites (Spalinger et al. 2007).

BLLs can rise 1–5 µg/dL for every 1,000-ppm increase in soil lead (U.S. EPA 2006a).

Dust. Dusts are composed of fine particles of soil, paint, and industrial or automotive emissions. They accumulate on exposed surfaces and are trapped in clothing and carpet fibers. Ingesting dust particles is the typical route of lead exposure for children (U.S. EPA 2006a). Dust is absorbed more readily than either paint or soil; house dust levels best predict children's BLLs (Lanphear et al. 1998c). Consequently, regulations for lead abatement and remediation have included dust clearance standards that quantify lead concentrations [Department of Housing and Urban Development (HUD) 1999; U.S. EPA 2006c].

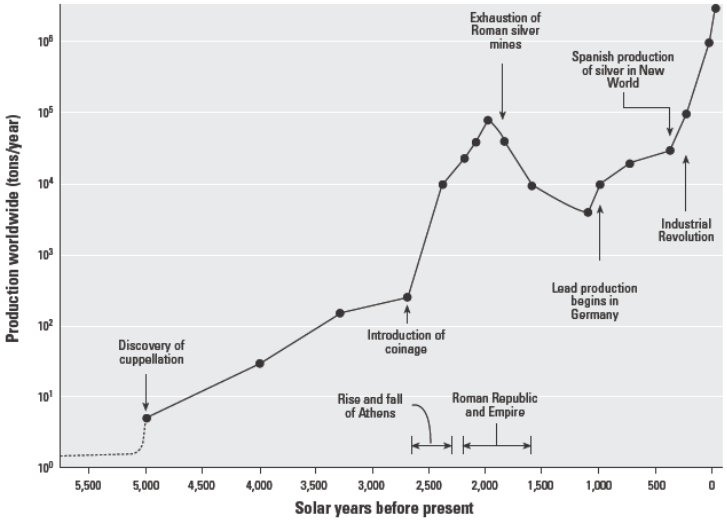

Figure 1. Increases in lead production and corresponding increases in lead emissions. Data from Davidson and Rabinowitz (1992) and U.S. EPA (1986).

BLLs can rise 1–5 µg/dL for every 1,000-ppm increase in dust lead (U.S. EPA 2006a).

Lead in the diet. The sources of lead in food may be natural or anthropogenic, and contamination can occur at any point in processing through contact with metal implements, solder, pigments, glazes, or packaging. Lead also enters food from drinking water, serving utensils, and household dust. Dietary exposures in the United States are 1–4 µg lead per day [U.S. Food and Drug Administration (FDA) 2006a], and have remained fairly constant during the past decade. Foreign manufacturers who fail to meet U.S. standards can produce contaminated food.

Breast milk. Lead in breast milk is related to current maternal exposures and to past exposures mobilized from lead stored in bones (Chien et al. 2006). Even low levels of lead in breast milk strongly influence an infant's BLL (Ettinger et al. 2006). Calcium supplementation can reduce lead in breast milk. In a randomized trial, calcium supplements lowered BLLs in lactating women with past high lead exposure and low dietary calcium intake (Hernandez-Avila et al. 2003). The benefits of breastfeeding outweigh concern for lead at BLLs common among U.S. women (Lawrence 1997).

Drinking water. Lead is unlikely in source water but contaminates tap water through the corrosion of plumbing materials containing lead (Chin and Karalekas 1985; Levin 1986). Lead pipes are more likely to be found in older homes. In new homes, legally "lead-free" plumbing components can contain up to 8% lead (Safe Drinking Water Act Amendments of 1986). New plumbing leaches lead more readily than older fixtures, where mineral scale covers internal surfaces. The largest unaddressed sources of lead in water are brass or chrome-plated fixtures and illegal use of lead solder (U.S. EPA 2006b).

Cases of pediatric lead poisoning have been associated with drinking water (CDC 1994; Cosgrove et al. 1989; Shannon and Graef 1989). BLLs correlate with drinking water lead levels even in populations with low exposures (Lanphear et al. 1998b). Sampling drinking water to determine exposure is difficult, and it is easy for sporadic or short-term elevations to go undetected (Schock 1999). Hence, exposure to lead from drinking water may be underestimated (Testud et al. 2001).

Changing or introducing secondary disinfection practices (to kill waterborne pathogens) can affect lead levels in drinking water. After Washington, DC, switched disinfection agents, children in homes with lead service lines did not experience the almost 70% decrease in BLLs > 5 µg/dL experienced by other children (CDC 2004c). Children with lead service lines also had considerably higher BLLs (32% > 5 µg/dL vs. 23% citywide) (CDC 2004c). Another study of changing disinfectants found that both water lead and BLLs increased (Miranda et al. 2007).

Lead levels in school drinking water can rise because long periods of nonuse (overnight, weekends, vacation) are followed by heavy consumption (Bryan 2004). The U.S. EPA has developed guidelines to help schools manage lead in their drinking water (U.S. EPA 2006d).

Drinking water contributes an estimated 10–20% of the total lead exposure of the general population (U.S. EPA 1991); formula-fed infants can have higher exposures. Drinking-water lead levels > 15 ppb are associated with a 14% increase in the percentage of children with BLLs > 10 µg/dL (Lanphear et al. 1998b).

Chocolate. Lead levels in chocolate products exceed those in other foods. In 1980, the market basket Total Diet Study (TDS) by the FDA found lead levels in chocolate milk more than three times those in whole milk, and levels in milk chocolate candy approximated those in canned foods (Pennington 1983). In the 2004 TDS, chocolate bars had the highest lead levels of the 280 items surveyed (FDA 2006a). A 2005 study comparing lead concentrations and isotopic compositions of cocoa beans grown in Nigeria with finished candy products found levels 60 times higher in finished candy versus cocoa beans (Rankin et al. 2005). No single source of lead was identified; levels rose at each stage of production.

Candy. Candy imported from Mexico is found repeatedly with high lead levels. Both candy and wrappers printed with lead ink have been cited (CDC 2002a; FDA 1995; Lynch et al. 2000; North Dakota Department of Health 2004). Lead-contaminated candy has also been imported from the Philippines and from Asian and Latin American countries. EBL cases have been reported in California, New York, North Dakota, Oklahoma, and Texas. In California, in 2001, candy was identified as a possible lead source for > 150 children with EBLs. In November 2006, the FDA reduced its recommended maximum lead level for candy consumed by children from 0.5 ppm to 0.1 ppm (FDA 2006b).

Imported foods. Foods and packaging produced outside the United States can contain high lead levels. Several spices (Sattar et al. 1989; Woolf and Woolf 2005), especially Hungarian paprika, have been contaminated (Kakosy et al. 1996). Food coloring also has been implicated in children's EBLs (Vassilev et al. 2005). In 2006, California sued PepsiCo and Coca-Cola Co. concerning lead in the labels of bottles brought to the United States from Mexico (Lifsher 2006).

Dietary supplements. An assessment of 84 dietary supplements found lead in all, with 11 samples exceeding the tolerable dietary lead intake level (Dolan et al. 2003). These results

Table 1. Lead used in Massachusetts manufacturing, 2003.

Activity/facility type	No. of facilities	Total use (lb)
Municipal waste combustors	7	2,642,987
Wire and cable manufacturing	21	2,622,713
Rubber and plastics manufacturing	10	1,856,941
Hazardous waste facilities	1	714,118
Fabricated metals manufacturing	22	363,406
Chemicals and allied products	12	304,619
Primary metals manufacturing	8	157,742
Electronic equipment manufacturing	37	119,651
Others	134	503,451
Total	252	9,285,628

Data from Massachusetts Department of Environmental Protection (2005).

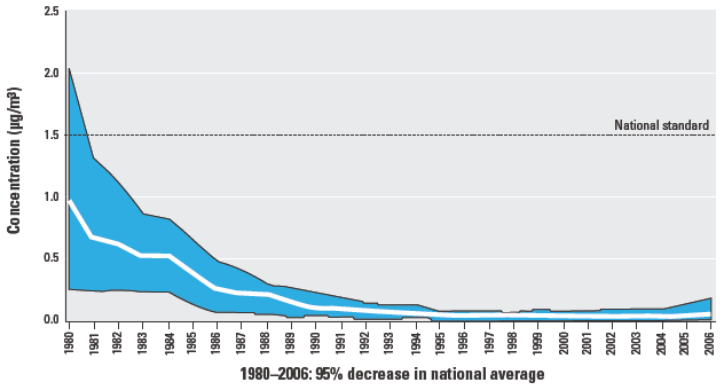

Figure 2. Maximum quarterly mean air lead concentrations, 1980–2006, showing 95% decrease 1980–2003 and slight increase 2004–2006; national trend based on 15 sites. Reprinted from U.S. EPA (2007a).

correlate with other FDA data (Hight et al. 1993; Wong et al. 2004). Other herbal supplements associated with high levels of lead include nettle (FDA 2002) and supplements to treat hair loss (Health Canada 2004).

The Dietary Supplement Health and Education Act prevents the FDA from requiring premarket safety approval for supplements; hence, they require neither proof of safety nor efficacy (Marcus and Grollman 2002). The FDA recently proposed good manufacturing practice regulations to help ensure the safety of dietary supplements (FDA 2003b) and is developing a final rule.

Glass and dishes. Leaded crystal contains 24–32% lead oxide. Crystal decanters and glasses can release high amounts of lead in a short time, especially with cola (Guadagnino et al. 2000). The FDA has cautioned that children and pregnant women should avoid frequent use of crystal glassware and should not use lead crystal baby bottles (Farley 1998).

Ceramic pottery and other dinnerware containing lead glazes can be important exposure sources. Numerous reports of EBLs associated with homemade or low-fired ceramics from Mexico, southern Europe, North Africa, and the Middle East exist (Hellstrom-Lindberg et al. 2006; Manor and Freundlich 1983; Matte et al. 1994). Relatively new, commercially manufactured ceramic dinnerware has also been cited (CDC 2004a). The FDA has established criteria for leachable lead in ceramics ranging from 0.5 to 3.0 μg/mL, depending on the product (FDA 2005c).

Glassware with decals or painted surfaces can also contain lead (Sheets 1999). In 1979, the FDA and the U.S. glassware industry established a voluntary quality control program for decorated glasses that contain lead (FDA 1992). Since 1994, the FDA has exempted ornamental ceramicware from lead-leaching requirements if it contains a permanent marking warning "for decorative use only" (FDA 1992). A complete listing of dishware restricted for importation is available (FDA 2007b).

Vinyl lunchboxes. The U.S. FDA advised manufacturers and suppliers that lead in soft vinyl lunchboxes (FDA 2006c) may transfer to food. Thus, it could be deemed an unsafe food additive (under Section 409 of the Federal Food Drug and Cosmetic Act) (FDA 2008) and adulterated within the meaning of Section 402(a)(2)(C) of the statute and subject to regulation.

Lead in consumer goods. According to the Consumer Product Safety Commission (CPSC), lead is the most frequently recalled substance that could result in poisoning. Many products associated with childhood lead poisoning are imported and do not meet U.S. standards (CDC 2002a; Geltman et al. 2001). A listing of all CPSC-recalled items is available (CPSC 2007). Products containing wood, metal, plastic, ceramics, and paper have been found with high lead concentrations.

Children's products. Consumer goods with high lead content are found regularly. One study showed that 94% of plastic bread bags contained lead in the printing ink; a survey of families found that 16% reused bags to package children's lunches (Weisel et al. 1991). In March and April 2007, CPSC issued recalls of 2,500 children's painting easels, 128,700 toy sets, 400,000 key chains, 58,000 children's necklaces, and 4 million children's bracelets because of lead content. In August and September 2007, Mattel Inc. alone recalled 2.8 million lead-contaminated toys (Denver Post 2007). All of these items were made in China.

A study of toy jewelry found lead concentrations ≥ 50% in 40% of samples (Maas et al. 2005); when wiped, 70% of these samples released at least 1.0 μg lead, enough to cause high exposure with little handling. The scope and frequency of the recalls suggest that the current nonregulatory approach to controlling lead in children's products could be strengthened.

Polyvinyl chloride (PVC). Lead salts are used to stabilize polymers to avoid degradation from heat, sunlight, and wear. Although several studies demonstrate that dangerous lead exposures can occur with normal use of PVC products after extended use or exposure to sunlight, initial evaluation by CPSC found that lead in PVC products posed few risks to children (CPSC 1997).

An investigation of vinyl miniblinds found that they contaminate house dust and contribute significantly to lead toxicity in children (Norman et al. 1997; West et al. 1998). Because about 30 million sets are sold annually and the polymers degrade under normal conditions, this might be a lead exposure source for millions of children, particularly those living in manufactured housing commonly equipped with miniblinds.

Since 1977, the water pipe market has more than doubled, and 80% of new drinking water and wastewater pipes are plastic, mostly PVC (Vinyl News Service 2006). Early tests of PVC pipes showed that lead contamination could be high (National Academy of Sciences Safe Drinking Water Committee 1982). Despite a standardized testing procedure for plastic pipes to reduce the potential for high lead exposures [Mitchener 1992; NSF/ANSI (American National Standards Institute) 2008; U.S. EPA 2007e], reports of dangerous exposures from plastic pipes continue (Koh et al. 1991).

Artificial Christmas trees made of PVC also degrade under normal conditions (Maas et al. 2004). About 50 million U.S. households have artificial Christmas trees, of which about 20 million are at least 9 years old, the point at which dangerous lead exposures can occur. High lead levels have also been found in telephone cords (Abdul-Razzaq et al. 2003).

Synthetic turf. Synthetic turf is currently used on about 3,500 playing fields throughout the United States (Claudio 2008). Rubber infill or crumbs made from recycled tires keep the turf blades upright, and this rubber can contain lead. The exposure potential, especially on older fields that have accumulated dust and where the materials are deteriorating, is a research gap.

Candle wicks. Candles with a lead metal core contribute to lead in the home (Nriagu and Kim 2000; van Alphen 1999). Exposure occurs both from air and from hand-to-mouth activity. However, to date, no children's EBLs traceable to candles have been reported. In 2002, the CPSC banned candlewicks containing > 0.06% lead (CPSC 2003).

Lead paint in housing. Approximately 38 million homes had lead-based paint (LBP) in 2000 (Jacobs and Nevin 2006). Of those, an estimated 24 million units had deteriorated lead paint, dust lead, or bare soil contaminated with lead (Jacobs et al. 2002). Of those with LBP hazards, 1.2 million units housed low-income families with children < 6 years of age. A relatively small number of properties may account for large numbers of children with EBLs (Korfmacher and Kuholski 2007; Meyer et al. 2005; Reyes et al. 2006).

Housing units with LBP hazards are not evenly distributed (Jacobs et al. 2002). In 2000, for households with incomes ≤ $30,000—the federal poverty level at that time—35% of the housing units had LBP hazards compared with 19% of all housing units. Northeast and Midwest housing has twice the prevalence of LBP hazards compared with housing in the South and West. Although the prevalence of LBP hazards increases with the age of the building, most painted surfaces, even in older housing, do not have lead paint; only 2–25% of building components have LBP (Jacobs et al. 2002).

Children in units with LBP are almost 10 times more likely to have an EBL than children in similar housing without lead paint (Schwartz and Levin 1991). Addressing lead paint hazards significantly reduces the risk of identifying another child with an EBL in a unit where one was previously identified (Brown et al. 2001a).

Mean BLLs of children whose housing was abated show a 38% decrease over a 2-year period after lead hazard control (National Center for Healthy Housing and the University of Cincinnati Department of Environmental Health 2004). Nonetheless, disturbing lead painted surfaces can increase the BLLs of children living in those units during repair work unless appropriate controls are

instituted, especially dust clearance levels (Amitai et al. 1991; Bellinger et al. 1986; HUD 1995). Studies of well-conducted renovation activities show that although lead hazard interventions reduce most children's BLLs, about 10% of the time BLLs significantly increased (CDC 1997; Clark et al. 2004); young children (< 18 months of age) are at highest risk of increases. BLLs of children who continued to live in the house or relocated for less than the full work period also were significantly more likely to increase than those of children who relocated for the entire renovation. Consequently, remediation and abatement activities that disturb lead paint must be followed by specialized cleaning and dust-lead testing to determine whether the unit is safe for re-occupancy.

Risk Factors for EBLs in U.S. Children

Between 1976 and 2002, the National Health and Nutrition Examination Surveys (NHANES) identified a constellation of risk factors for EBLs among children. Previously undocumented risk factors continue to be uncovered in urban areas and within particular subpopulations (Dignam et al. 2004). Nationally representative samples do not identify or characterize local risks. The CDC recommends that states target communities with the highest risk for lead exposure, using established risk factors (CDC 2003).

Age. Children's BLLs peak around 15–24 months of age (Tong et al. 1996). This age dependence persists even as average BLLs have decreased. Given the pervasive lead contamination of our environment, it is not surprising that normal hand-to-mouth behaviors result in high exposures among toddlers. Young children also absorb lead more readily than do older children and adults. Exposures with little effect on adults cause high levels in young children (Faustman et al. 2000).

Race and ethnicity. The NHANES show an association between BLLs and race/ethnicity (Figure 3). In 1976–1980, the geometric mean BLL for all U.S. children was 16 µg/dL versus 21 µg/dL for black children (Mahaffey et al. 1982). Data from 1999–2002 show similar patterns: 46.8% of non-Hispanic black children and 27.9% of Mexican-American children exceeded 5 µg/dL compared with 18.7% for white children (CDC 2005b). Fortunately, the gap is narrowing. The most recent national data show that non-Hispanic black children had the largest decline in BLLs (72%) of all racial and ethnic groups, reducing the differences between subpopulations (Jones R, personal communication).

Use of ethnic remedies, cosmetics, and goods. Folk medicines and remedies from many cultures can contain high lead levels (Baer and Ackerman 1988; Trotter 1985). Traditional Mexican remedies were the earliest focus (CDC 2002a), but poisonings in six states and one death have been linked to Ayurveda, a traditional South Asian medicine (CDC 1984, 2004d; Moore and Adler 2000). Imported herbal remedies are available at many local markets (Saper et al. 2004). Ethnic and imported cosmetics and other goods have also been associated with high lead exposures (CDC 2005c; Sprinkle 1995).

Immigrant or refugee status. Refugee, internationally adopted, and recent immigrant children are more likely than U.S.-born children to have EBLs, both on arrival in the country and later (Geltman et al. 2001; Miller and Hendrie 2000; Tehranifar et al. 2008). Many foreign children enter the United States with EBLs resulting from lead sources in their native countries. Their BLLs rise after resettlement because of both lead contamination in their new environments and continued use of imported products containing lead. Existing health burdens and cultural, language, and economic barriers compound the risk for lead poisoning after resettlement. For example, iron deficiency, prevalent among refugee children, increases lead absorption through the gastrointestinal tract. Exposure to small amounts of lead can result in very high BLLs in iron-deficient children (Stauffer et al. 2002; Weissman 1994).

An increased risk for EBLs has been documented among refugee and immigrant children from Africa, Cuba, China, Russia, Thailand, and other countries (CDC 2005a; Mielke et al. 1984; Trepka et al. 2005). For instance, although there were only 46 cases of EBLs in Manchester, New Hampshire, in 1997, there were 88 in 2004; all the additional EBLs were among African-born children. In 2003, the CDC found that 45% of refugee children had elevated BLLs a few months after resettlement (CDC 2005a). BLLs are often elevated in school-age and teenage foreign-born children. The CDC recommends testing refugee and immigrant children on entry to the United States and again 3–6 months later, mirroring policies established by New Hampshire's CLPPPs after a fatality in 2000. The CDC also recommends nutritional evaluation and intervention for deficiencies.

Income level. Children with EBLs are more common in communities with many households below the federal poverty level, independent of housing age or proportion of black children (Bernard and McGeehin 2003; Sargent et al. 1995). In 1976–1980, children with the lowest family income had an average BLL of 20 µg/dL versus 16 µg/dL nationally (Mahaffey et al. 1982). In Massachusetts in 1991–1992, the 15 communities with > 25% of children ≤ 5 years old living in poverty accounted for 71% of children with BLLs ≥ 25 µg/dL (Sargent et al. 1995).

Income-based disparities of EBLs in children have narrowed. In 1991–1994, the percent of children with EBLs was 4.5% in the lowest income group versus 0.7% in the highest income group (Pirkle et al. 1994). By 1999–2002, the difference between the percent of Medicaid-enrolled children with EBLs and the general population was not statistically significant (1.7% vs. 1.3%, respectively). However, the geometric mean BLL for Medicaid-enrolled children exceeds unenrolled children, indicating continued disparity in lead exposures (2.6 µg/dL vs. 1.7 µg/dL) (CDC, unpublished data).

Age of housing. Housing built before the 1978 ban on lead paint is a significant risk factor for exposure. Forty-two percent of children living in housing built before 1946, and 39% of children in housing built between 1946 and 1973 had BLLs ≥ 5 µg/dL versus 14% of children in housing built after 1973 (Bernard and McGeehin 2003).

Location of residence. Children 1–5 years of age living in the 10 largest U.S. cities accounted for 46% of EBLs reported to the CDC in 2003 but only 7% of the population that age (CDC, unpublished data). Usually, EBL cases are clustered within cities. A 2001 study of seven cities found that 50% of children with EBLs lived in 11% of the ZIP codes in those cities (Brown et al. 2001b).

Lead contamination typically is greater in urban versus rural areas (National Research Council 1993; U.S. EPA 2006a). Although long-distance transport of lead does occur, many studies show that most of the lead emitted in urban areas remains there (Flegal et al. 1989). The discrepancy between BLLs of urban and rural children has remained

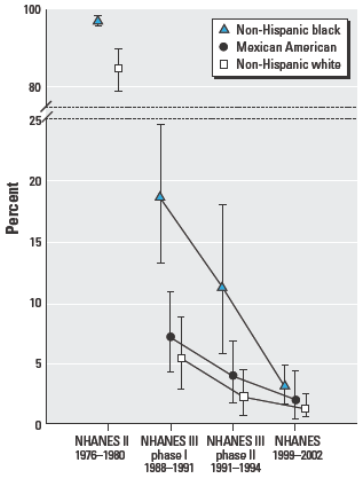

Figure 3. Percentage of U.S. children, 1–5 years of age, with EBLs ≥ 10 µg/dL (95% confidence intervals), by race/ethnicity. Data from CDC (2005b).

constant despite the decline in overall lead exposures for U.S. children since the late 1970s (Brody et al. 1994).

Parental occupations. Lead dust from work inadvertently carried by parents settles on surfaces and workers' clothing, where it can be ingested or inhaled by young children (Hipkins et al. 2004). Children of lead-exposed workers have disproportionately higher BLLs (Chan et al. 2000; Whelan et al. 1997). Based on 1981–1983 survey data, an estimated 48,000 families with children < 6 years of age had a household member who worked with lead (Roscoe et al. 1999). Concern for take-home exposure is not new; two studies from the early 1900s identified severe poisonings of workers' families, including case histories from 1860 (Holt 1923; Oliver 1914).

Many occupations with potential high lead exposures are exempted from Occupational Safety and Health Administration workplace protections, including transportation workers, most public employees, and self-employed workers in industries such as battery reclamation, automobile repair, pottery and ceramics, and stained glass. Undocumented workers are particularly vulnerable because of limited access to exposure monitoring and protective measures.

Other risk factors. **Season of the year.** BLLs are significantly higher in warm weather in both national and local studies (Kaufmann et al. 2000; U.S. EPA 2007c). The relation persists despite the decline in lead exposure. Several factors may explain seasonal variations: greater exposures to soil lead, dispersion of dust when lead-painted windows are opened and shut (Haley and Talbot 2004), and remobilization of lead on interior surfaces as air moves through open windows and doors. In warmer weather, children's longer hours outdoors may increase exposure to airborne and soil lead and contribute to seasonality in BLLs (Yin et al. 2000). Changes in Vitamin D exposures during the warmer weather may also account for some of the seasonality observed (Kemp et al. 2007).

Tobacco smoke. Having a smoker in the house has been associated with higher BLLs in children for 30 years (Willers et al. 1988; Zielhuis et al. 1978). Cotinine levels still correlate positively with BLLs (Mannino et al. 2003).

Implications for Lead Poisoning Prevention

The current CDC advisory level for intervention in individual children is 10 µg/dL (CDC 1991). It is not a safe level; studies show strong and long-lasting effects with BLLs as low as 2 µg/dL. Therefore, the CDC recommends primary prevention—that is, that all lead sources in children's environments be controlled or eliminated before children are exposed.

Achieving the Healthy People 2010 objective—to reduce BLLs as much as possible and to eliminate childhood lead poisoning— will require collaboration by all levels of government. This cannot succeed without enforcing all existing standards, ensuring that ambient lead levels continue to decline, and reversing recent trends of increased lead exposures, such as air lead and imported consumer goods. Table 2 summarizes federal authorities for regulating lead.

Addressing lead paint hazards. Lead-based paint in housing remains the most common high-dose source of lead in children's environments. Reducing lead hazards in housing requires

- Data to be shared across organizational boundaries
- Local and state regulatory requirements for lead-safe housing
- Strengthened enforcement of existing laws, especially cleanup
- Greater public and private investment for lead hazard control.

Some of the most hazardous residential units may not be eligible for HUD's Lead Hazard Control program because they are uninsured, have outstanding taxes, have other serious code violations, or because the owner cannot be located. In this case, emergency funds are needed to raze buildings that cannot reasonably be made safe.

Evidence that primary prevention is effective is mounting. For example, a project initiated in 1998 by HUD, assisted by the Department of Justice, the CDC, and the U.S. EPA, to enforce Title 1018 of the Toxic Substances Control Act has resulted in commitments to make over 185,000 high-risk properties lead-safe by 2006 (Gant J, HUD, personal communication).

Identifying all sources of lead exposure. Local CLPPPs remain the frontline in identifying lead exposure sources. As particular lead paint hazards are controlled or eliminated, other lead sources assume greater importance and visibility. The CDC recommends that when children with EBLs are identified, CLPPPs identify all sources of lead in the child's environment (CDC 2002b).

Research is needed on effective intervention strategies for children with BLLs above average but < 10 µg/dL to prevent dangerous exposures.

Table 2. U.S. lead regulatory authorities.

Agency	Lead source regulated	Statutory authority	Voluntary
CPSC	Paint /coatings	CPSC 1977	None
	Candle wicks	CPSC 2003	None
	Lead in products intended for use by children	None	CPSC 2008
FDA	Food/materials that contact food (domestic)	FDA 2004a	None
	Lead in bottled water	FDA 2003a	None
	Prescription and over-the-counter drugs	FDA 2004b	None
	Dietary supplements	Proposed rule (FDA 2003b)	None
	Seizure of imported food, drugs, and cosmetics	FDA 2003c	None
	Candy	None	FDA 2006a
	Ceramics/pottery	None	FDA 2005a
	Shellfish	None	FDA 2005b
	Wine	None	FDA 2007a
	Soft vinyl lunchboxes	None	FDA 2006b
U.S. EPA	Drinking water	U.S. EPA 1991	None
	Plumbing components, school drinking water	U.S. EPA 1988, 2007c	U.S. EPA 2008a
	Air	U.S. EPA 2008b	None
	Lead paint disclosure, renovation/repair, and clean up	U.S. EPA 1992, U.S. EPA 2006c	None
	Waste management, disposal	U.S. EPA 1980a, U.S. EPA 1980b	None
HUD	Residential lead paint hazards in federally subsidized properties	HUD 1999	None
	Disclosure of lead paint at property transfer	HUD 1992	None
OSHA	Worker protection for general industry	OSHA 2008a	None
	Construction industry	OSHA 2008b	None
NSF/ANSI	Plumbing codes, plumbing components	Local and state housing and plumbing codes	NSF/ANSI 2008 U.S. EPA 2007e

Maintaining lead-safe communities. Creating lead-safe communities can occur only with the active involvement of all levels of government—local, state, and federal—and will depend on several strategies. Foremost are systems that monitor and evaluate all children's potential lead exposures. Other keys to institutionalizing primary prevention are requirements for lead-safe housing and work practices, dust- and soil-lead testing after repairs in older housing, identification of all lead sources for children with EBLs, elimination of products with dangerous lead levels, and timely mechanisms to share information about lead sources, including toxic properties, across government agencies.

State and local officials should evaluate whether their existing primary prevention efforts sufficiently protect children.

Federal agencies should support local and state efforts by

- Monitoring lead in air, drinking water, food, and consumer products
- Enforcing laws that control lead contamination
- Educating specific populations about lead and controlling exposures
- Improving exposure modeling techniques, accounting for all sources of exposure
- Conducting research and ongoing evaluation of lead poisoning prevention activities.

Conclusions

The Healthy People 2010 objective to eliminate BLLs ≥ 10 μg/dL is within our grasp. The course is clear. We must identify and address all existing lead hazards and be vigilant in preventing new hazards. Recent research describes the enormous societal benefits to be reaped from preventing lead exposure in children (Grosse et al. 2002; Landrigan et al. 2002; Nevin et al. 2008), with total annual estimates of $43–110 billion or more. The overall reduction of lead in the environment will benefit all U.S. children—and adults, too.

Correction

In "Sources of Lead Exposure," the percentages given for types of sources were incorrect in the manuscript originally published online. They have been corrected here.

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EXHIBIT 3

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ORIGINAL ARTICLE

The impact of drinking water, indoor dust and paint on blood lead levels of children aged 1–5 years in Montréal (Québec, Canada)

Patrick Levallois[1,2], Julie St-Laurent[1], Denis Gauvin[1], Marilène Courteau[1], Michèle Prévost[3], Céline Campagna[1], France Lemieux[4], Shokoufeh Nour[3], Monique D'Amour[4] and Pat E. Rasmussen[4]

Lead is neurotoxic at very low dose and there is a need to better characterize the impact of domestic sources of lead on the biological exposure of young children. A cross-sectional survey evaluated the contribution of drinking water, house dust and paint to blood lead levels (BLLs) of young children living in old boroughs of Montréal (Canada). Three hundred and six children aged 1 to 5 years and currently drinking tap water participated in the study. For each participant, residential lead was measured in kitchen tap water, floor dust, windowsill dust and house paint and a venous blood sample was analyzed. Multivariate logistic regression was used to evaluate the association between elevated BLL in the children (≥ 75th percentile) and indoor lead contamination by means of odds ratios (OR) using 95% confidence intervals (CI). There was an association between BLL ≥75th percentile (1.78 μg/dL) and water lead when the mean water concentration was >3.3 μg/L: adjusted OR = 4.7 (95% CI: 2.1–10.2). Windowsill dust loading >14.1 μg/ft^2 was also associated with BLL ≥1.78 μg/dL: adjusted OR = 3.2 (95% CI: 1.3–7.8). Despite relatively low BLLs, tap water and house dust lead contribute to an increase of BLLs in exposed young children.

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Keywords: blood lead levels; children; paint; dust; drinking water

INTRODUCTION

Lead is a known toxicant that can have health effects at very low levels, and young children are particularly vulnerable to its deleterious effects. Evidence of subtle neurotoxic effects at blood lead levels below 10 μg/dL have been reported.[1,2] Despite important actions to remove lead sources (such as leaded gasoline and lead soldering) from the general environment, lead exposure continues to be an important issue. Indoor sources of lead are still present in children's surrounding environment and might contribute to low levels of exposure. This is particularly the case for sources such as house dust, paint or drinking water.[3,4]

Lead service lines (pipes) and lead containing materials are well-known sources of drinking water contamination.[5] However, the impact of low levels of lead contamination in drinking water has been rarely studied. Recently, two studies conducted in the Washington DC area[6,7] described the impact of lead service lines on BLLs of young children. However, because of limitations concerning the evaluation of children's water exposure, their results could not precisely quantify the impact of lead from drinking water on BLLs.

Lead in paint and house dust remains an important source of lead exposure. In the United States, the contribution of old paint as a source of lead exposure for young children is well documented.[8] Some cases of lead poisoning from paint have been described in Canada[9] but no population study has yet evaluated the impact of lead-based paint on young children in a non point-source area. In the US, the importance of low-level house dust on BLLs of young children has been well demonstrated in an analysis of NHANES data.[10] The importance of lead-based paint as a key cause for elevated indoor dust lead concentration was described in a recent nationally representative study of house dust in urban homes across Canada.[11]

As a number of sources are likely to be present simultaneously in the home environment, particularly in old houses, it is important to evaluate them at the same depth, in order to quantify their individual contributions. In fact, most of the studies done on the impact of these sources on BLLs of children have only considered one source[6,7,10] or have evaluated one source in greater depth than the others.[12]

In 2005, moderate concentrations of lead were reported in tap water of Montréal households connected with lead service lines (LSLs).[13,14] The resulting potential increase of BLLs of young children was then estimated using the US EPA IEUBK model by the Montréal Public Health Department (MPHD) and found to be lower than the current Québec BLL notification level of 10 μg/dL.[14] Since no case of lead poisoning related to drinking water was reported in the area and considering that many families were still using tap water for young children (despite advice from the MPHD to do the contrary), this site appeared highly suitable to quantify the impact of tap water exposure on BLLs and compare it to other lead sources.

The objective of this study was therefore to evaluate the impact of drinking water and other household sources of lead such as house dust and paint, on the BLLs of children aged 1–5 years and living in households where LSLs may still be present.

[1]Institut national de santé publique du Québec, Québec, Canada; [2]Centre de recherche du Centre Hospitalier Universitaire de Québec and Université Laval, Québec, Canada; [3]École Polytechnique de Montréal, Montréal, Canada and [4]Health Canada, Ottawa, Canada. Correspondence to: Dr. Patrick Levallois, Institut national de santé publique du Québec, 945, avenue Wolfe, QC, Canada G1V 5B3.
Tel: +(418) 650 5115 (ext 5216). Fax: +(418) 654 3144.
E mail: patrick.levallois@msp.ulaval.ca
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METHODS

General Methodology

This cross sectional study simultaneously evaluated the BLLs and home indoor environment of young children (1 to 5 years of age) living in four boroughs of Montréal, selected for the possible presence of lead pipes and older houses. The study was carried out between September 2009 and March 2010.[15] The ethics committees of the Center hospitalier universitaire de Québec and Health Canada approved the protocol developed for this study. Parents of children participating in the study provided their written informed consent prior to their participation.

Recruitment and Participant Selection

Following exclusion of industrial areas, a randomly selected list of 9,500 families, with at least one child aged 1 to 5 years and living in the targeted boroughs, was obtained from the Québec government's health database (*Régie de l'Assurance Maladie du Québec*). After excluding families living in buildings with more than 3 dwellings, an information letter and a consent form were sent to 3,800 families living in the targeted boroughs. Only one child per family was pre selected. The participant's parents were contacted by telephone to verify the child's eligibility and their willingness to participate in the study. Families meeting the following criteria were classified as eligible (*n* 549): the selected child consumes tap water regularly, was born in Canada, and was living in that dwelling for at least one year; he or she does not spend more than 2 days per week outside of the home or suffer from severe disease; the family should speak either French or English and does not use a water filtration device. Detailed frequencies of eligibility parameters for included and excluded families for this study are described and enumerated in Supplementary Materials (Supplementary Tables S1 and S2).

Home Visit

A trained environmental technician and a pediatric nurse visited each home. Following the completion of the consent form by one of the parents, the technician conducted a house inspection, water and dust sampling, and paint evaluation. The nurse interviewed the parents about their work and hobbies, the child's health and habits (including water consumption and pica behavior) and drew a venous blood sample from the child's arm.

Blood Sample

Venous blood was sampled in a 6 mL Becton Dickinson tube (BD 367863) pre treated with Ethylenediaminetetraacetic acid (EDTA) anticoagulant and kept at 4 °C until laboratory analysis. Whole blood samples were analyzed for lead content by Inductively Coupled Plasma Mass Spectometry (ICP MS), using the Perkin Elmer Elan 6000 at the laboratory of the Institut National de Santé Publique du Québec (INSPQ, Québec, Canada). The detection limit was 0.02 μg/dL and the quantification limit was 0.08 μg/dL. Internal quality control was conducted using three reference materials obtained from the INSPQ (External Quality Assessment Schemes) (1.87 μg/dL, 6.25 μg/dL and 30 μg/dL). Duplicates performed every 10 analyses had a mean correlation coefficient of 0.992.

Tap Water

A total of 5 one liter samples of cold kitchen tap water were collected in pre acidified containers. The first liter was sampled following a 5 min flush (5M1L) at typical flow (5 to 7 L/min). After a 30 min stagnation period, 4 consecutive liters (30M1L, 30M2L, 30M3L, 30M4L) were sampled. Participants were asked not to use any source of water within their homes during the period of stagnation. The tap aerator was kept on during all sampling.

Samples were held at approximately 4 °C until analysis. Water lead analyses were performed using ICP MS with Single Ion Monitoring (SIM) by an accredited environmental laboratory (Maxxam). The analysis protocol used was similar to that outlined in US EPA Method 200.8[16] with a slight increase in holding time of the acidified sample (i.e. increased from 16 to 24 h to enhance dissolution of particulate lead). The detection limit for the method was 0.01 μg/L and the quantification limit was 0.015 μg/L. Quality control was regularly performed during the analysis period (blank, certified reference material, duplicate, and fortified blank). The correlation coefficient for duplicates was 0.999. Results obtained for fortified blanks were within the limits used by this laboratory.

Dust

Floor dust was sampled from a selected sampling zone in the center of the available floor space in three different rooms in the home: the child's room, home entrance and another room specified by the parents as frequently used by the child. A one square foot on smooth surface was sampled with a disposable wet wipe (Ghost wipes, Delta Scientific, #SC4250) following a standardized method (ASTM E 1728 03).[17] Dust on the windowsill in the child's room was collected with a separate wet wipe and sampling surfaces were measured to express results in $\mu g/ft^2$. Each wet wipe was placed individually in plastic tubes and kept at 4 °C until laboratory analysis. To assure the absence of external contamination, two different wipe controls were used for each sampling zone: (1) a control wet wipe (in one out of every two residences,) was manipulated outside the plastic tube but without wiping on a surface and, (2) a template sampling using the regular protocol (once a week) on the interior surface of a template.

Analyses of the lead dust wipes consisted of predigesting the wet wipe in a partially covered 50 mL tube with 2 mL of concentrated nitric acid at room temperature for 5 h. The digestion tube was then placed in a bath at 80 °C for 12 h. Afterwards, the tube was withdrawn from the bath, and when it reached room temperature, 1 mL hydrochloric acid was added and a total volume of 10 mL was achieved by adding deionised water. Analysis was done by ICP MS (Elan 6000, Perkin Elmer, Massachusetts, USA). Calibration was performed using aqueous standards. The detection limit was 0.01 μg and the quantification limit 0.015 μg per sample.

Paint

The lead content of the interior painted surfaces of homes was evaluated with a hand held X ray fluorescence (XRF) analyzer (Niton XLp300, Elemental Controls, Mississauga, Ontario, Canada). Sampling procedure, adapted from the US Department of Housing and Urban Development (US HUD),[18] consisted of taking two consecutive 30 second measurements, a few centimetres apart. Where lead content was equal to or greater than 0.5 mg/cm^2, a third measurement was performed for confirmation. Where there were different paints in one room, more than one wall was sampled. At least five rooms were assessed according to the child's use and/or the level of deterioration of painted surfaces (child's room, kitchen, family room, hallway and one other room commonly used by the child). The calibration of the XRF analyzer was verified 3 times before each home measurement with a standard reference material (Niton XLp300 Performance Characteristic Sheet 2004).

Where wall paint chips were present on damaged surfaces or flooring, they were collected for laboratory analysis. Approximately 200 mg of paint chips were necessary for lead analysis. Samples were digested at room temperature for 2 h in a partially covered test tube containing 2 mL of concentrated nitric acid. Afterwards, samples were covered and placed in an oven at 110 °C for 18 hours. Analyses were performed using ICP MS method (Elan 6000, Perkin Elmer). Certified standard reference material paint chips from the National Institute of Standards and Technology (NIST 1579A) and demineralized water reference material from Ultra Scientific (ICM 240) were used for calibration and quality control. The detection limit was 10 μg/g and the quantification limit was 30 μg/g.

Statistical Analyses

BLL was considered both as a continuous and a categorical variable. When treated as a continuous variable, BLL measures are summarized as a geometric mean (GM) since the distribution of measurements is close to lognormal. When treated in categories, an elevated BLL was defined as a BLL equal or greater than the 75th percentile of measurements from the 306 participating children ($\geq$1.78 μg/dL). Environmental exposure variables were treated in tertiles, except for paint where a qualitative division was used according to the XRF evaluation and the lead content of paint chips collected. Participants with missing values for windowsill dust were excluded from the analysis concerning only windowsill dust. Otherwise, these participants were pooled in a fourth category of windowsill dust: the "missing" category (the first 3 categories being the tertiles of the variable).

Two types of univariate analyses were performed in order to select variables to include in the multivariate logistic regression model for BLLs above the 75th percentile (with all exposure variables treated in categories). First, the GM of BLLs was calculated for each exposure variable (drinking water, dust and paint) and adjustment variables (listed below). For dichotomous variables, Student's *t* test of the blood lead logarithm was used to compare the means; for variables with three categories or more an analysis of variance was used. The source of

difference between means, when a statistical difference was observed, was determined using Scheffe's test for multiple comparisons. Chi square tests were performed to determine variables with a significant relationship with elevated BLLs ($\geq 1.78\,\mu g/dL$).

Exposure variables, adjustment variables with P value ≤ 0.15 in one of the univariate analysis, or variables known to influence BLLs were included in the full multivariate logistic regression model after testing for multicolli nearity (diagnostic of multicollinearity for variables with Variance Inflation Factor >2.5)[19] (See Supplementary Material, Table S3). The adjustment variables were then withdrawn from the full model if their withdrawal did not change the OR of the exposure variables by more than 10%.

Possible modifying effects of seasons (fall or winter) and daycare use on exposure variables were then tested, as well as the interaction between the exposure variables. A tested effect was kept in the model if its P value was <0.05. The adjustment variables included in the final multivariate logistic regression model were: age, ethnicity (Caucasian or not), season, parents' highest education level (one parent with a university degree), daycare use, health issue (chronic disease), exposure to second hand smoke, possible parental lead exposure from occupation or hobbies, and tap water consumption per kg of body weight (food and beverage consumption as reported by the parents). No modifying effects were found significant in the logistic regression model. The adjusted results are presented in two different ways. First, the model was run separately for each exposure variable and with all the adjustment variables (adjusted OR). Second, the model was run with all the exposure variables and all the adjustment variables (adjusted + OR). In this second model, the dust variables were included only for the evaluation of the effect of water and paint exposures.

SAS software version 9 for Windows (Copyright (c) 2002 2008 by SAS Institute Inc., Cary, NC, USA) was used to perform the statistical analyses. The statistical significance level for the multivariate analysis was set at 0.05.

RESULTS

Participation Rate

Of the 3,800 families contacted by letter, 2,661 were reached by phone to verify their eligibility. Of the 549 eligible families identified, 313 (57%) accepted the invitation to participate in the study. Only 306 families were included in the data analysis, since no blood sample could be collected for 6 children, and one child was absent from their dwelling for an entire month prior to the home visit.

Participant Characteristics

The majority of participants were classified as Caucasian (i.e. not included in a visible minority group as defined by Statistics Canada[20]) and spoke French at home (Table 1). Most families owned the residence investigated and were highly educated, with 73% having at least one parent with a university degree. Only 5% of children had a severe risky behavior for lead exposure, defined as scratching, licking or gnawing soldered surfaces or paint. Most children were healthy, except a few (6%) who had moderate chronic disease such as asthma (data not shown). Daycare service was used by 75% of participants. Finally, only a few parents were evaluated as being possibly exposed to lead during their work (8%) or hobbies (10%).

Environmental Source of Exposure

The GM concentration of lead in the kitchen tap water was $0.89\,\mu g/L$ after 5 min flushing (Table 2). The arithmetic mean (AM) of the 5 tap water samples (our main exposure variable) was first calculated for each sampling event. The GM of all sampling events was then determined to be $1.60\,\mu g/L$. The GM for each of the stagnation (30 M) samples was calculated and the highest mean concentration of lead in tap water was observed in the first liter after 30 min of stagnation ($1.91\,\mu g/L$). Concentrations of total lead exceeded $10\,\mu g/L$ in only 5 residences after 5 min of flushing and in 37 households after 30 min stagnation (data not shown).

The GM lead loading was $0.85\,\mu g/ft^2$ for floor dust (AM of 3 samples) and $7.14\,\mu g/ft^2$ for lead in windowsill dust. A total of 9 floor dust samples and 4 windowsill dust samples exceeded for a total of 12 residences the current US EPA regulatory requirements[21] of $40\,\mu g/ft^2$ for floor dust and $250\,\mu g/ft^2$ for windowsill dust. Between one and 11 paint chips were collected from each residence for 157 participants. The median concentration of lead in paint chips was 1,300 mg/kg. Forty-two residences (27%) had lead concentrations higher than the 5,000 mg/kg US HUD guideline for paint chips (data not shown). Also, 31% of the residences evaluated had painted structures with 2 or more XRF measurements exceeding the $1\,mg/cm^2$ US HUD guideline. Of these houses, 3% had more than 4 different painted structures exceeding the $1\,mg/cm^2$ criteria. There was a weak, but significant ($P<0.05$) correlation between floor dust and windowsill ($r=0.272$) and floor dust and paint ($r=0.214$), as shown in Supplementary Material, Table S4.

Blood Lead Levels

The GM concentration of BLLs for all children was $1.35\,\mu g/dL$ (Table 3) and ranged from $0.37\,\mu g/dL$ to $19.06\,\mu g/dL$. Only one

Table 1. Characteristics of the participants and their families.

Characteristics	n *(%)*
Children sociodemographic characteristics	
Age (month)	
12 23	50 (16)
24 35	66 (22)
36 71	190 (62)
Gender	
Girl	153 (50)
Boy	153 (50)
Visible minority[a]	
Yes	99 (32)
No	207 (68)
Children life habits	
Risk behaviors [b]	
None	153 (50)
Moderate	138 (45)
Severe	15 (5)
Daycare use	
Yes	229 (75)
No	77 (25)
Parents' sociodemographic characteristics	
Owner status	
Owner	183 (60)
Renter	123 (40)
Parents' highest education level[c]	
University	221 (73)
Other	83 (27)
Spoken language	
French	267 (87)
English	39 (13)
Possibility of lead exposure	
Parent occupational exposure	
Yes	25 (8)
No	281 (92)
Hobbies exposure at home[d]	
Yes	31 (10)
No	275 (90)

[a]Visible minorities as defined by Statistics Canada: African, Asian, Arab, Latin American or Caribbean descent. [b]Severe risk behaviors are defined as involving scratching, licking or gnawing soldered surfaces or paint; Moderate risk behaviors include the habit of placing different objects in the mouth, such as fingers, toys, sand or grass. [c]Data missing for 2 participants. [d]Hobbies considered were: making lead shots, lead fishing weights, stained glass, figurines or decorative objects containing lead or lead solder, welding, pottery, jewelry, ceramics, miniature models (using glue), or activities such as glass blowing, hunting, recreational shooting, and stripping paint from old furniture, vehicles or boats.

child had a lead concentration above of the Québec notification level (10 μg/dL). Children classified in the non-Caucasian group had higher BLLs (1.53 μg/dL) compared to Caucasians (1.27 μg/dL), BLLs were higher in children of parents not holding a university diploma (1.52 μg/dL) compared to measurements of children where one or more parents had a university diploma (1.30 μg/dL). BLLs were higher in fall than in winter (1.50 μg/dL compared to 1.27 μg/dL) but no measurements were taken in either spring or summer. The differences in BLL concentrations between the above groups were statistically significant ($P<0.05$). Similar associations were found when considering children with elevated BLLs (Table 3).

Association of BLLs with Lead Indoor Contamination

After adjusting for risk factors of elevated BLL, including ethnicity, season and water consumption, all four lead exposure variables were found to be associated with BLLs ≥75th percentile (Table 4). However, when the ORs were also adjusted for the other studied lead exposure variables (adjusted+), only the OR in the third tertiles of lead in tap water and lead in windowsill dust remained statistically significant: Adjusted+ OR for water = 4.7, 95%CI: 2.1–10.2, and of windowsill dust (adjusted+ OR: 3.2, 95%CI: 1.3–7.8). A sensitivity analysis revealed that the relationship between water contamination and elevated BLLs was not different if we considered as the exposure variable: the 5 min flushed sample (OR = 3.9; 95%CI: 1.8–8.6), the mean of the first and second liters after 30 min stagnation (OR = 4.5; 95%CI: 2.0–10.0) or the mean of the third and fourth liters after stagnation (OR = 3.7; 95%CI: 1.7–7.9) (See Supplementary Material, Supplementary Table S5). This relationship was similar after stratifying the participants by season of sampling but this was not the case for the other exposure variables where the relationship with elevated BLL was mostly present only during winter (See Supplementary Material, Supplementary Table S6). However, no significant statistical interactions were found between those variables and the season.

DISCUSSION

Lead exposure in children remains an important issue. Given the reduction of lead exposure via external sources such as gasoline, the impact of indoor sources might be relatively more important nowadays. Our results appear to demonstrate that even with a very low background of lead exposure, and low contamination in the home environment, sources such as water and home dust can still have a detectable impact on the BLLs of young children.

Lead Indoor Contamination

Results obtained for fall and winter sampling showed low lead concentrations in kitchen tap water for the majority of participants, with a mean concentration of 1.60 μg/L which is well below the Québec standard of 10 μg/L and lower than water concentrations reported in earlier BLLs studies.[6,22] The lead loading of residential house dust was low but comparable to results from similar studies. In particular, the lead loading of house dust in our study was consistent with values recently reported in the large 2007-2008 NHANES database with mean lead loads in floor and windowsill dust of 0.52 and 7.64 μg/ft^2 respectively.[23] Our dust results are slightly higher than those found in another Canadian study reporting that 3 out of 222 houses located in Ontario had lead content of floor dust wipes exceeding the US EPA criteria[21] of 40 μg/ft^2 (compared to 9/306 in our study).[24]

Lead-based paint was frequently present in older houses (built in 1920–1949) in our study. In particular, about 27% of our participants were exposed to paint chips containing ≥5,000 mg/kg lead and 31% were living in houses with painted structures exceeding the US HUD criteria of 1 mg/cm^2, as analyzed by XRF. These measured concentrations are similar to those reported in other North American studies[25,26] but higher than those observed by Lanphear *et al.*[27] Lead paint contamination is a common source of indoor dust lead contamination which is supported in this study by a weak correlation between lead in paint and house dust (See Supplementary Material, Supplementary Table S4).

BLLs and their Relationship with Indoor Contamination

Blood lead levels found in the studied children were low and comparable to those reported recently in North America. For instance, in the 2007-2008 NHANES study, the geometric mean of the BLL of 817 children aged 1–5 years was estimated to be at 1.5 μg/dL,[28] which compares with results from this study, and in particular to results from the fall period.

Despite the low levels of contamination, we report an impact of the indoor environment on BLLs of young children, which is especially significant for very moderate lead contamination in tap water (>3.27 μg/L) and windowsill dust (>14.14 μg/ft^2). The

Table 2. Distribution (percentiles and mean) of lead concentration by source of exposure.

Exposure variables	*Percentiles*			*GM (95% CI)*
	10th	*50th*	*90th*	
Kitchen tap water (μg/L) (n 306)				
5M1L	0.16	1.24	4.51	0.89 (0.77, 1.04)
30M1L	0.44	2.33	7.05	1.91 (1.69, 2.16)
30M2L	0.31	2.24	7.39	1.66 (1.45, 1.90)
30M3L	0.24	1.99	7.39	1.55 (1.33, 1.80)
30M4L	0.25	1.90	10.06	1.53 (1.30, 1.80)
AM of 5 samples[a]	0.30	2.08	7.51	1.60 (1.40, 1.84)
Dust (μg/ft^2)				
Floor (n 305)	0.19	0.70	4.70	0.85 (0.73, 0.98)
Windowsill (n 263)	1.06	7.15	50.89	7.14 (5.84, 8.73)
Paint (mg/kg)				
Paint chips (n 157)[b]	15	1,300	24,000	

Abbreviations: 5M1L: first liter after 5 min flushing; 30 M, after 30 min of stagnation; 1L, first liter; 2L, second liter; 3L, third liter; 4L, fourth liter; AM, arithmetic mean; CI, confidence interval; GM, geometric mean.
[a]Arithmetic mean of the 5 kitchen tap water samples (1 liter after 5 min flushing and 4 consecutive liters after 30 minute stagnation). [b]Highest concentration of lead in paint chip per home.

relationship with water contamination was the most robust and remains significant when the different types of water samples were considered. The contribution of lead contamination in water to BLL has been studied previously, mostly in populations exposed to higher lead concentrations.[5] In Washington, DC, Brown *et al.*[7] assessed the impact of the presence of LSLs and of changes in the type of disinfectant used (chlorine vs chloramines) to the BLLs of young children between the years 1986 and 2006. They reported that children aged 0–3 years served by a LSL were more likely to be situated in the upper fourth quartile of BLLs, especially during peak lead release periods. Important differences hinder the direct comparison of our results with those from Brown *et al.*[7] First and

Table 3. Distribution (percentiles and mean) of blood lead (μg/dL) according to the sociodemographic characteristics of children and the season of sampling.

	Percentiles of BLL				*GM (95% CI)*	*% of BLLs (≥1.78 μg/dL)*
	10th	*50th*	*75th*	*90th*		
Age (Month)						
12 23	0.75	1.27	1.76	2.69	1.32 (1.14, 1.53)	20.0
24 35	0.68	1.40	1.91	3.11	1.41 (1.24, 1.60)	33.3
36 71	0.80	1.31	1.72	2.49	1.34 (1.24, 1.44)	21.6
All	0.77	1.31	1.78	2.69	1.35 (1.27, 1.43)	25.0
Visible minority[a]						
No	0.73	1.26	1.68	2.28	1.27 (1.18, 1.37)	21.3
Yes	0.81	1.37	1.91	3.32	1.53* (1.38, 1.69)	29.3
Gender						
Girl	0.77	1.33	1.80	2.90	1.39 (1.28, 1.51)	25.5
Boy	0.73	1.26	1.74	2.49	1.31 (1.20, 1.42)	22.2
Parents' highest education level						
University	0.77	1.26	1.68	2.49	1.30 (1.21, 1.39)	20.8
Other	0.81	1.41	2.07	3.11	1.52** (1.36, 1.70)	32.5**
Sampling season[b]						
Fall	0.85	1.43	2.01	3.11	1.50** (1.36, 1.66)	31.2*
Winter	0.73	1.20	1.60	2.28	1.27 (1.18, 1.37)	19.8

Abbreviations: BLLs, blood lead levels; CI, confidence interval; GM, geometric mean.
[a]Visible minorities as defined by Statistics Canada: African, Asian, Arab, Latin American or Caribbean descent. [b]Fall season was set from September 10 to December 15, and Winter was set from December 16 to March 27. *$P<0.005$. **$P<0.05$.

Table 4. Crude and adjusted odds ratios of blood lead levels according to the lead concentration in the lead exposure sources (water, lead or paint).

Exposure source	n	*Crude OR (95% CI)*	*Adjusted*[a] *OR (95% CI)*	*Adjusted+*[b] *OR (95% CI)*
Kitchen tap water[c] *(n 306)*				
1. <0.75 μg/L	101	1.00 ( )	1.00 ( )	1.00 ( )
2. 0.75 3.27 μg/L	105	1.37 (0.65 2.91)	1.55 (0.68 3.57)	1.24 (0.52 2.93)
3. >3.27 μg/L	100	4.14* (2.07 8.28)	5.07* (2.37 10.82)	4.66* (2.12 10.24)
Floor dust[d] *(n 305)*				
1. <0.45 μg/ft^2	102	1.00 ( )	1.00 ( )	1.00 ( )
2. 0.45 1.22 μg/ft^2	103	1.36 (0.67 2.74)	1.10 (0.52 2.35)	0.95 (0.44 2.09)
3. >1.22 μg/ft^2	100	2.46* (1.26 4.80)	2.56* (1.26 5.21)	2.06 (0.97 4.40)
Windowsill dust (n 263)				
1. <3.54 μg/ft^2	86	1.00 ( )	1.00 ( )	1.00 ( )
2. 3.54 14.14 μg/ft^2	90	2.37* (1.10 5.10)	2.40* (1.04 5.54)	2.18 (0.90 5.28)
3. >14.14 μg/ft^2	87	2.63* (1.23 5.64)	3.15* (1.38 7.23)	3.22* (1.33 7.79)
Paint[e] *(n 306)*				
1. XRF <1 mg/cm^2	121	1.00 ( )	1.00 ( )	1.00 ( )
2. XRF ≥1 mg/cm^2 or Paint chips <5,000 mg/kg	143	1.11 (0.59 1.92)	1.06 (0.55 2.04)	0.92 (0.45 1.86)
3. Paint chips ≥5,000 mg/kg	42	2.61* (1.23 5.57)	3.30* (1.44 7.56)	2.28 (0.90 5.76)

Abbreviations: BLLs, blood lead levels; CI, confidence interval; OR, odds ratios; XRF, X ray fluorescence analyses.
[a]OR adjusted for age, ethnicity, season, parents' highest education level, daycare used, moderate chronic disease, second hand smoke exposure, possible parental lead exposure from occupation or hobbies and tap water consumption/bw. [b]OR adjusted+ for all variables in [a](adjusted OR) and for the other lead exposure variables (ie., Tap water, adjusted for floor dust, windowsill dust and paint; Paint, adjusted for tap water, floor dust and windowsill dust; Floor dust and windowsill dust, adjusted for tap water and paint). [c]Arithmetic mean of the 5 kitchen tap water samples (1 liter after 5 min flushing and 4 consecutive liters after 30 minute stagnation). [d]Arithmetic mean of 3 floor dust samples. [e]Highest concentration of lead in paint chip per home. *p<0.05, compared to the first tertile.

foremost, tap water and BLL samples were not paired at the individual level as in this study. Furthermore, tap water samples were collected using different protocols (greater stagnation time of 6 hours) which typically increases the lead concentration in analyzed water samples.

The impact of house dust moderately contaminated by lead was clearly demonstrated in this study for children living in homes with elevated dust lead loadings on window sills $>14.14\,\mu g/ft^2$ and to a lesser extend on floors ($>1.22\,\mu g/ft^2$). Our results are in agreement with those of the 1999-2004 NHANES data presented by Dixon *et al.*[10] In the NHANES study, BLLs of children (at levels $\geq 5\,\mu g/dl$ and $10\,\mu g/dl$) aged 1–2.5 years living in pre-1978 housing were associated with a dose-response with lead load of floor house dust ranging from about $0.5\,\mu g/ft^2$ to about $40\,\mu g/ft^2$.[10] However, despite similarities between our study and the Dixon study, we should consider that the latter study used only one floor wipe sample which may have contributed to greater measurement uncertainty with respect to dust lead loading.

The impact of leaded paint (the presence of paint chips with lead load $\geq 5{,}000$ mg/kg) on elevated BLLs was also demonstrated in this study, although this association did not remain statistically significant when considering other lead exposures from tap water and dust. However, possible over-adjustment is acknowledged due to the likely contribution of lead paint to floor dust. Leaded paint is still considered as a major source of lead poisoning in young children.[9,29] Other associations between leaded paint and elevated BLLs of young children have been observed in Chicago children,[30] but not in the Rochester study.[27]

Limits

Despite its strengths (no point source of lead in the selected boroughs, indoor lead-targeted boroughs, systematic recruitment, in-depth evaluation of the major components of residential exposure and high quality control for data collection and laboratory measurements), our study has some limitations that should be discussed. In particular, due to its cross-sectional design, this study was not able to evaluate the precise environmental exposures which occurred in the months before obtaining a child's blood sample. Since the half-life of BLL is about one month,[31] the effect of the recent exposure history is particularly important. Seasonal variations relate to both environmental exposure to lead,[32,33] and to the tendency for BLLs to be higher in warmer period (e.g. summer).[32,34] This is partly reflected in this study by the higher BLLs observed during the fall season compared to winter. However, a Supplemental analysis demonstrated that, despite higher BLLs in the fall, the association between lead in tap water and elevated BLLs measured by the OR was quite stable in both studied seasons. However, this was not the case for the other studied exposures. We could not identify precisely the levels of home contamination that occurred during the summer season and its association with elevated BLLs. We also did not take into account the exposure that could occur outside the home as well as the direct or indirect effect of nutrition status.

CONCLUSION

The results of this study demonstrate that, despite relatively low contamination, all the lead exposure sources in the domestic environment that we have evaluated (water, dust, and paint) contribute to the elevation of BLLs in children of 1 to 5 years of age, living in targeted areas of Montréal. Dust and paint were well known contributors to lead poisoning in the past and their effect on BLLs of children is still present. Drinking water flowing through lead service lines is not a negligible source of exposure to lead and may be a persistent significant contributor to children's BLL. Given the absence of a known health effects threshold for exposure to lead, studies on risk factors and drivers of exposure in groups of children with low exposure are still important to guide strategies for further reducing low-level exposures to lead.

ABBREVIATIONS

AM, Arithmetic mean; BLL, Blood Lead Level; CI, Confidence interval; GM, Geometric mean; OR, Odds ratio; 5M1L, First liter after 5 min flushing; 30M1L, First liter after 30 min stagnation; 30M2L, Second liter after 30 min stagnation; 30M3L, Third liter after 30 min stagnation; 30M4L, Fourth liter after 30 min stagnation

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Journal of Exposure Science and Environmental Epidemiology website (http://www.nature.com/jes)

EXHIBIT 4

Lead Intoxication in Infancy

Michael W. Shannon, MD, MPH,*‡§ and John W. Graef, MD‡§

ABSTRACT. Four years of experience in the evaluation and management of lead intoxication in the first year of life were reviewed. This study was conducted in a lead referral program within the state of Massachusetts, whose comprehensive lead laws include extensive (and now mandatory) lead screening of all children. Over the period of study, 50 (14%) of 370 new patients enrolled in the program were infants aged 12 months or younger. Median age of these infants was 11 months (range 1 through 12 months). Mean peak lead level was 39.0 μg/dL while the mean peak erythrocyte protoporphyrin concentration was 111.9 μg/dL of whole blood. Thirty-two percent of infants were ambulatory at the time lead intoxication was diagnosed; only 24% had a history of pica. Twenty-six percent of parents were welfare dependent. Apparent sources of plumbism included household renovation (n = 20), direct ingestion of paint chips (n = 10), formula preparation with lead-contaminated water (n = 9), lead dust importation (n = 1), and congenital exposure to elevated maternal lead level (n = 1). In 9 cases the source was not found. When this profile was compared with that of a randomly selected group of 47 children aged 18 through 30 months, who were seen in the lead program during the same interval, apparent sources of intoxication in the older group were paint chip ingestion (n = 41), household renovation (n = 2), and unknown (n = 4) ($P < .0001$). On the basis of these data, it is concluded that lead intoxication in infants is common and has significantly different origins from that in toddlers. Lead intoxication from infant formula reconstituted with contaminated water may account for many of these cases. These findings support recommendations that lead screening begin at the age of 6 months for children with any likelihood of lead exposure. *Pediatrics* 1992;89:87–90; *lead intoxication, infant, screening.*

Lead is one of the most widespread environmental toxins facing American children. Well-controlled studies continue to accumulate evidence that, even at what were once considered low levels of exposure, apparently irreversible adverse health effects, particularly to the central nervous system, occur in young children.[1–4] The increasing concern about children with lower levels of lead exposure has forced a reexamination of the epidemiology of this disease. Data from 1950 to 1980 focused attention on the ambulatory toddler, 12 to 36 months of age, living in older, usually dilapidated housing, in whom high blood levels of lead developed after ingestion of paint chips (pica).[5] Lead poisoning in infants was considered a rarity, usually resulting from unique circumstances such as inappropriate use of lead-based body cosmetics or direct administration of lead-containing folk medicines.[6,7] This view has had several unfortunate consequences: (1) it discourages pediatricians from initiating lead screening until the second year of life; (2) it discourages lead screening of children from rural and suburban areas where dilapidated housing is less common; and (3) when plumbism is discovered, it is assumed the intoxication is the result of pica and alternative sources of lead are not investigated.

Little is known about the prevalence and pattern of lead poisoning in infants. The Second National Health and Nutrition Examination Survey (1976 to 1980) included children from age 6 months but the sample size was small and results were included in the data of children up to age 2 years.[8] However, since 1978 the Centers for Disease Control has recommended screening high-risk children beginning at 6 months of age.[9] The American Academy of Pediatrics, while noting that some children might be at risk as early as 6 months of age, has recommended initial screening to coincide with the first routine hematocrit at 9 to 12 months.[6] The Commonwealth of Massachusetts has offered voluntary statewide lead screening for children from age 1 year up to 6 years since the passage of its Lead Poison Prevention Act in 1971. A revision of this law in 1987 included a provision for mandatory screening according to a schedule to be determined by state public health authorities in consultation with interested medical groups. This schedule included the requirement that children at "high risk," as determined by the likelihood of direct exposure to lead hazards, be screened at least every 6 months, beginning at 6 months of age.

We recently noted a significant number of young infants being referred to our Lead/Toxicology Program, perhaps in part because of the increasing surveillance of Massachusetts children of all ages. Therefore, we undertook this study to examine more closely the patterns of childhood plumbism seen in Massachusetts in the first year of life.

METHODS

For this study, the hospital charts of all patients through the age of 12 months seen in the Lead/Toxicology Program of The Children's Hospital, Boston, from 1987 through 1990 were reviewed. While this clinic is a referral program for the evaluation and management of children with any environmental intoxication, re-

From the *Division of Emergency Medicine and ‡Program in Clinical Pharmacology/Toxicology, The Children's Hospital, Department of Pediatrics, Harvard Medical School, and §The Massachusetts Poison Control System, Boston.

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Reprint requests to (M.W.S.) Children's Hospital, 300 Longwood Ave, Boston, MA 02115.

ferrals of children with plumbism predominate. With occasional exceptions, children with lead intoxication were eligible for enrollment if their venous blood lead levels exceeded 25 μg/dL of whole blood. This value was reduced in 1990 to accept children with lead levels exceeding 20 μg/dL.

At the initial clinic visit, a thorough environmental history was obtained which included previously recorded lead levels, a description of the patient's residence, results of any environmental inspections (paint, water, and/or soil analysis), blood lead levels of siblings, recent renovation, oral habits of the child, recent changes in behavior, time spent elsewhere, occupations of both parents, water sources, and water intake. For infants younger than 11 months of age, a detailed history of formula preparation practices was also obtained.

Laboratory assessment of patients included measurement of whole blood lead and erythrocyte protoporphyrin concentrations; complete blood and reticulocyte counts; serum iron level; total iron-binding capacity (TIBC); ferritin, blood urea nitrogen, and serum creatinine levels; and urinalysis. Blood and water lead analyses were performed by atomic absorption spectrophotometer (Perkins-Elmer Corp, Norwalk, CT). Radiographic evaluation on the first clinic visit usually included knee and abdominal radiographs (for evaluation of growth arrest lines or radiopaque gastrointestinal densities). On the basis of these data and after state-mandated inspection of the home for lead hazards, a judgment of the likely source of lead was made and medical management (including education on preventing further exposure) was provided.

To compare the origins and clinical profile of infants with that of older children managed in our program, we randomly selected (on the basis of alphabetical listing) 47 children aged 18 through 30 months who attended the Lead/Toxicology Program during the same study interval, extracting similar demographic and clinical data.

Statistical comparisons were conducted by using the Student's *t* test, χ^2 with Yates' continuity correction, the Mann-Whitney *U* test, and analysis of variance with the Scheffe post hoc multiple comparisons procedure. Normally distributed data are expressed as mean ± SD.

RESULTS

Over the 4-year period, of 370 new patients enrolled in the Lead/Toxicology Program, 50 (14%) were infants. Twenty-seven were girls and 23 were boys. Median age of these patients was 11 months (range 1 through 12 months). Six infants aged 1 through 7 months were identified after their older siblings were found to have plumbism. Socioeconomic status as indicated by hospital payer classification revealed 33 patients (66%) with private insurance and no stated reliance on public welfare. Only 26% received Medicaid or other public assistance.

No patients had clinical signs of lead intoxication. Sixteen infants (32%) were ambulatory at the time lead poisoning was diagnosed. Twelve infants (24%) had a history of pica (excessive oral habits which included repeated ingestion of nonfood objects).

Mean peak whole blood lead level was 39.0 ± 11.4 μg/dL. Thirteen infants had a peak lead level >50.0 μg/dL. Mean peak erythrocyte protoporphyrin level was 111.8 ± 90.9 μg/dL.

Iron status was assessed by the combination of hemoglobin level, hematocrit, mean corpuscular volume, serum iron levels, TIBC, and serum ferritin levels. Twenty-five patients (50%) had hemoglobin levels of <11.5 g/dL, 28 (56%) had hematocrit of <34%, and 14 (32%) patients had a serum iron-TIBC ratio of <16%. Serum ferritin level was depressed in 20 (40%) patients based on age-specific normal values for The Children's Hospital. Girls had a significantly higher hemoglobin level than boys (11.6 g/dL vs 11.1 g/dL, $P = .04$).

Five distinct origins of lead intoxication were identified: household renovation, ingestion of paint chips, formula preparation, dust importation, and congenital (Table 1).

Twenty cases occurred as a result of household renovation. Renovation was invariably done without knowledge of the lead content of the house; a parent was usually the renovator. In the two cases in which paint was removed with a heat gun, all family members including both parents and siblings were tested and found to have increased lead levels (range 18 to 60 μg/dL).

Ten cases occurred as a result of pica. Seven of these cases were notable for the witnessed ingestion of paint chips. All 10 children in this group were walking before the age of 10 months. However, the abdominal radiograph identified radiopaque material in only two infants at the time of evaluation.

Nine cases of plumbism were traced to the preparation of powdered or concentrated infant formula with lead-contaminated water (Table 2). Three distinct patterns of hazardous formula reconstitution were identified: (1) use of contaminated tap water which had been boiled for 10 to 20 minutes (n = 5); (2) use of either tap or spring water which was boiled in a leaded vessel (n = 3); and (3) use of contaminated first-draw, unboiled morning water to make the day's supply of formula (n = 1). In seven of these cases, exposure was confirmed by analysis of the water used to prepare the formula and the exclusion of other available lead sources. Water lead concentrations as high as 200 000 parts per billion were found in the confirmed cases.

When cases were dichotomized into formula-associated cases (9) vs non-formula-associated cases (41), there was no significant difference in peak blood lead level (38.9 vs 39.3 μg/dL), but significantly lower hemoglobin level (10.8 g/dL vs 11.6 g/dL, $P = .02$), hematocrit (32.3% vs 34.2%, $P = .05$), serum iron-TIBC ratio (0.156 vs 0.294, $P = .008$), and ferritin level (20.5 ng/mL vs 36.3 ng/mL, $P = .011$) were found in children with lead intoxication from contaminated formula. This difference persisted when all discrete routes of exposure were compared with formula-associated cases by analysis of variance.

One case each of plumbism occurred as a result of dust importation by a parent who worked extensively with lead and by placental passage of maternal lead. In the case of dust importation, the father, a private contractor, was found to have a blood lead level of 70 μg/dL after lead intoxication was identified in the infant. The case of congenital lead intoxication occurred in a newborn whose adolescent mother devel-

TABLE 1. Identifiable Sources of Lead Poisoning

Source	No. (%)
Household renovation	29 (49)
Paint chip ingestion	10 (24)
Formula preparation	9 (24)
Work clothing	1 (2)
Congenital	1 (2)
Total	41 (100)

TABLE 2. Cases Resulting From Formula Preparation With Lead-Contaminated Water

Case	Age, mo	Confirmed	Peak PbB,* μg/dL	Lead Source	[Pb], ppb
1	4	–	31	Boiled water	
2	4	–	30	Boiled water	
3	9	+	21	Boiled water	142
4	9	+	47	Boiled water	1.0×10^3
5	9	+	41	Boiled water	117
6	9	+	55	Lead vessel	3.5×10^3
7	12	+	48	Lead vessel	1.7×10^3
8	12	+	57	Lead vessel†	2.0×10^5
9	12	+	40	Morning water‡	150

* PbB, blood lead concentration.
† Formula prepared with spring water only.
‡ Previously reported elsewhere.[19]

oped lead intoxication at age 2 but was never fully treated. The infant's blood lead level, obtained at the age of 1 month, was 31 μg/dL; the simultaneous maternal lead level was 40 μg/dL.

Among the 47 toddlers selected for comparisons, mean age was 23.8 ± 3.5 months. Peak lead level was 42.2 ± 16.8 μg/dL (P = not significant compared with infant lead levels). Compared with the infant population, there were no significant differences in distribution of payer status, hemogram, or iron indices. However, a higher rate of pica was reported in the older group (Table 3). The origins of lead intoxication in the older group were paint chip ingestion by history in 41 (87%), household renovation in 2 (4%), and unknown in 4 (9%). This distribution differed significantly from that in the younger infants ($P < .0001$).

DISCUSSION

The findings in this study suggest that the origins of lead intoxication in the first year of life differ considerably from those found in toddlers. These differences have important implications both for the identification of lead intoxication and appropriate environmental inspection for this age group.

The most common source of plumbism in infancy was found to be household renovation (49% of identifiable cases). Home renovation, when not being done for the purpose of deleading, has been identified as a significant predictor of elevated lead levels in children.[7,9] Use of heat guns and sanding create particularly toxic lead fumes or lead dust which are efficiently absorbed after ingestion and/or inhalation.[10]

Pica, long considered the most common mechanism of lead intoxication in children, accounted for only 24% of infant cases where the source could be identified. This is not surprising when one considers that the infant who is not yet ambulating and under close supervision has limited opportunities for the ingestion of paint chips. This low frequency stood in contrast to the 87% frequency found among the toddlers who attended our program.

TABLE 3. Origins of Lead Intoxication: Infants vs Toddlers*

Source	Infants, No. (%)	Toddlers, No. (%)
Renovation	20 (40)	2 (4)
Paint chip ingestion	10 (20)	41 (87)
Formula preparation	9 (18)	0
Work clothing	1 (2)	0
Congenital	1 (2)	0
Unknown	9 (18)	4 (9)

* $P < .0001$, Mann-Whitney.

The frequency of lead intoxication traced directly to formula preparation practices was surprising. A 10th infant has been identified since the completion of this study. The use of lead pipes for plumbing was standard until 1920, and lead-based solder was widely used in plumbing until 1984; these products were not banned from the plumbing industry until 1986.[5] Their ubiquity has created an almost inescapable lead hazard in our water supply. An estimated 10 400 000 children are exposed to significant amounts of lead through drinking water and 241 000 children younger than 6 years have lead levels greater than 15 μg/dL as a result of drinking such lead-contaminated water.[5,11–13] Recent actions by the Environmental Protection Agency to reduce the acceptable level of waterborne lead from 50 to 15 parts per billion have attempted to address this widespread problem.

Eight of the nine cases involved the practice of adding boiled water to powdered or concentrated formula. Powdered and concentrated infant formulas do recommend boiling water for 5 minutes, for the purpose of sterilization, before adding it to reconstitute these preparations (personal communication, Ross Laboratories, Columbus, OH). Excessive boiling, however, increases the lead concentration of tap water, amplifying the risk of lead intoxication and exposing the infants to substantial quantities of lead with every formula feeding.

Ceramic and pewter kitchenware are well-known sources of leachable lead.[6,14] However, in the three cases associated with lead-based kettles, the instruments were an antique copper-covered lead vessel, a cooking vessel brought from the Middle East, and a pot manufactured in the United States. The importation of leaded cooking vessels by immigrants may represent another unappreciated lead hazard.

The difference in iron status between the formula- and non-formula-poisoned children is of interest. The most plausible explanation would be that infants with formula-associated plumbism had inadequate iron intake throughout their period of lead exposure. The retrospective nature of this study did not permit complete details on use of normal- vs low-iron formula in these infants; in fact, when details were available,

a history of combined formula use was often present. However, because iron deficiency is known to increase gastrointestinal lead absorption, the presence of this nutritional deficiency would have been a significant contributor to the development of lead intoxication.

Even after detailed history and standard home inspection were conducted, the source of lead was unclear in 9 infants and 4 toddlers. There are several possible explanations for the inability to determine origin in these cases. One is that the Massachusetts standard home inspection, which required only paint analysis by x-ray fluorescence (a method with significant imprecision), may have missed other lead hazards. Alternatively, these cases may have occurred from outdoor activity with exposure to exterior paint or leaded soil (11 of these 13 cases of lead intoxication were identified between the months of June and September). Plumbism may have also occurred from unwitnessed episodes of pica. Finally, these cases may have been the result of normal oral activities within homes with high levels of lead-based dust; an estimated 34% of a child's typical daily lead dose originates from such dust even in the absence of pica.[15,16]

Little information on the prevalence of lead intoxication in infants is available. In Massachusetts 30 250 infants were screened for plumbism in 1990 (a screening rate of 35% based on the 85 000 births in the state in 1989). Of these, 46 (0.1%) were found to have whole blood lead levels of ≥25 μg/dL (personal communication, M. J. Brown, Massachusetts Department of Public Health). This is in contrast to a 1.1% incidence rate which has been found in 13- through 36-month-old children undergoing lead screening in Massachusetts in 1989.

In both age groups we found a high rate of lead intoxication among children of middle and upper socioeconomic strata. While this prevalence may represent referral patterns specific to our program and is therefore not generalizable, rates of lead intoxication in suburban areas as high as 30% have been reported in previous studies.[17,18]

These data support recent recommendations to initiate lead screening in children at 6 months. Highest priority should be given to children living in older, dilapidated housing, those whose homes have recently undergone renovation, and those who share environmental contacts with a child known to have plumbism. These children should receive venous lead measurements rather than erythrocyte protoporphyrin screening, given the insensitivity of erythrocyte protoporphyrin in detecting low-level lead exposures.

Finally, our findings suggest the need for systematic evaluation of potentially hazardous formula preparation practices. In addition to discussing common lead sources, child care providers should provide education on safe methods of formula preparation if all significant sources of lead are to be identified and avoided.

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EXHIBIT 5

Elevated Blood Lead Levels in Children Associated With the Flint Drinking Water Crisis: A Spatial Analysis of Risk and Public Health Response

Mona Hanna Attisha, MD, MPH, Jenny LaChance, MS, Richard Casey Sadler, PhD, and Allison Champney Schnepp, MD

Objectives. We analyzed differences in pediatric elevated blood lead level incidence before and after Flint, Michigan, introduced a more corrosive water source into an aging water system without adequate corrosion control.

Methods. We reviewed blood lead levels for children younger than 5 years before (2013) and after (2015) water source change in Greater Flint, Michigan. We assessed the percentage of elevated blood lead levels in both time periods, and identified geographical locations through spatial analysis.

Results. Incidence of elevated blood lead levels increased from 2.4% to 4.9% ($P < .05$) after water source change, and neighborhoods with the highest water lead levels experienced a 6.6% increase. No significant change was seen outside the city. Geospatial analysis identified disadvantaged neighborhoods as having the greatest elevated blood lead level increases and informed response prioritization during the now-declared public health emergency.

Conclusions. The percentage of children with elevated blood lead levels increased after water source change, particularly in socioeconomically disadvantaged neighborhoods. Water is a growing source of childhood lead exposure because of aging infrastructure. (*Am J Public Health.* 2016;106:283–290. doi:10.2105/AJPH.2015.303003)

See also Rosner, p. 200.

In April 2014, the postindustrial city of Flint, Michigan, under state appointed emergency management, changed its water supply from Detroit supplied Lake Huron water to the Flint River as a temporary measure, awaiting a new pipeline to Lake Huron in 2016. Intended to save money, the change in source water severed a half century relationship with the Detroit Water and Sewage Department. Shortly after the switch to Flint River water, residents voiced concerns regarding water color, taste, and odor, and various health complaints including skin rashes.[1] Bacteria, including *Escherichia coli*, were detected in the distribution system, resulting in Safe Drinking Water Act violations.[2] Additional disinfection to control bacteria spurred formation of disinfection byproducts including total trihalomethanes, resulting in Safe Drinking Water Act violations for trihalomethane levels.[2]

Water from the Detroit Water and Sewage Department had very low corrosivity for lead as indicated by low chloride, low chloride to sulfate mass ratio, and presence of an orthophosphate corrosion inhibitor.[3,4] By contrast, Flint River water had high chloride, high chloride to sulfate mass ratio, and no corrosion inhibitor.[5] Switching from Detroit's Lake Huron to Flint River water created a perfect storm for lead leaching into drinking water.[6] The aging Flint water distribution system contains a high percentage of lead pipes and lead plumbing, with estimates of lead service lines ranging from 10% to 80%.[7] Researchers from Virginia Tech University reported increases in water lead levels (WLLs),[5] but changes in blood lead levels (BLLs) were unknown.

Lead is a potent neurotoxin, and child hood lead poisoning has an impact on many developmental and biological processes, most notably intelligence, behavior, and overall life achievement.[8] With estimated societal costs in the billions,[9–11] lead poisoning has a disproportionate impact on low income and minority children.[12] When one considers the irreversible, life altering, costly, and disparate impact of lead exposure, primary prevention is necessary to eliminate exposure.[13]

Historically, the industrial revolution's introduction of lead into a host of products has contributed to a long running and largely silent pediatric epidemic.[14] With lead now removed from gasoline and paint, the incidence of childhood lead poisoning has decreased.[15] However, lead contamination of drinking water may be increasing because of lead containing water infrastructures, changes in water sources, and changes in water treatment including disinfectant.[16–18] A soluble metal, lead leaches into drinking water via lead based plumbing or lead particles that detach from degrading plumbing components. ("Plumbing" is derived from the Latin word for lead,

ABOUT THE AUTHORS

Mona Hanna-Attisha and Allison Champney Schnepp are with Hurley Children's Hospital/Michigan State University College of Human Medicine, Department of Pediatrics and Human Development, Flint, MI. Jenny LaChance is with Hurley Medical Center Research, Flint. Richard Casey Sadler is with Michigan State University College of Human Medicine, Division of Public Health, Flint.

Correspondence should be sent to Mona Hanna-Attisha, MD, MPH, FAAP, Hurley Medical Center, Pediatrics 3W, One Hurley Plaza, Flint, MI 48503 (e-mail: mhanna1@hurleymc.com). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

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"plumbum.") Lead was restricted in plumb ing material in 1986, but older homes and neighborhoods may still contain lead service lines, lead connections, lead solder, or other lead based plumbing materials. Lead solubility and particulate release is highly variable and depends on many factors in cluding water softness, temperature, and acidity.[19–21] The US Environmental Pro tection Agency (EPA) regulates lead in public water supplies under the Safe Drinking Water Act Lead and Copper Rule, which requires action when lead levels reach 15 parts per billion (ppb).

Lead in drinking water is different from lead from other sources, as it disproportion ately affects developmentally vulnerable children and pregnant mothers. Children can absorb 40% to 50% of an oral dose of water soluble lead compared with 3% to 10% for adults.[22] In a dose–response relationship for children aged 1 to 5 years, for every 1 ppb increase in water lead, blood lead increases 35%.[23] The greatest risk of lead in water may be to infants on reconstituted formula. Among infants drinking formula made from tap water at 10 ppb, about 25% would ex perience a BLL above the Centers for Disease Control and Prevention (CDC) elevated blood lead level (EBLL) of 5 micrograms per deciliter (μg/dL).[24] Tap water may account for more than 85% of total lead exposure among infants consuming reconstituted formula.[25] A known abortifacient, lead has also been implicated in increased fetal deaths and reduced birth weights.[26]

As recommended by the CDC and supported by the American Academy of Pediatrics, blood lead screening is routine for high risk populations and for children insured by Medicaid at age 1 and 2 years.[27] The CDC recommended screening ages are based on child development (increased oral–motor behavior), which places a child most at risk for house based lead exposure (e.g., peeling paint, soil, dust). State and national blood lead–screening programs, however, do not adequately capture the risk of lead in water because infants are at greatest risk.

Armed with reports of elevated WLLs and recognizing the lifelong consequences of lead exposure, our research team sought to analyze blood lead data before (pre) and after (post) the water source switch with a geographic information system (GIS) to determine lead exposure risk and prioritize responses. This research has immediate public policy, public health, environmental, and socioeconomic implications.

This research includes Flint, Michigan, and surrounding municipalities in Genesee County (Greater Flint). Greater Flint is a postindustrial region of nearly 500 000 people struggling from years of disinvestment by the automobile industry and associated manufacturing activities: the region has lost 77% of its manufacturing employment and 41% of employment overall since 1980.[28] National and local data sources demonstrate dismal indicators for children, especially within Flint city limits.[29–32] Greater Flint ranks toward the bottom of the state in rates of childhood poverty (42% in Flint vs 16.2% in Michigan and 14.8% in the United States), unemployment, violent crime, illicit drug use, domestic violence, preterm births, infant mortality, and overall health outcomes (81st out of 82 Michigan counties).

Greater Flint's struggles have been am plified by a history of racial discrimination, whereby exclusionary housing practices were common.[33,34] Such attitudes toward in tegration later precipitated White flight and emboldened home rule governance,[35,36] causing a massive decline in tax revenue for the city. The declining industrial and resi dential tax bases strained the city's ability to provide basic services and reversed the public health fortunes of the city and suburbs.[37] Severely reduced city population densities reduced water demand in the distribution system, exacerbating problems with lead corrosion.

METHODS

This retrospective study includes all chil dren younger than 5 years who had a BLL processed through the Hurley Medical Center's laboratory, which runs BLLs for most Genesee County children. The pre time period (before the water source change) was January 1, 2013, to September 15, 2013, and the post time period (after the water source change) was January 1, 2015, to September 15, 2015. The primary study group comprised children living within the city of Flint (n = 1473; pre = 736; post = 737) who received water from the city water system. Children living outside the city where the water source was unchanged served as a comparison group (n = 2202; pre = 1210; post = 992).

After institutional review board approval and Health Insurance Portability and Accountability Act waiver, we drew data from the Epic electronic medical record system including BLL, medical record number, date of birth, date of blood draw, full address, sex, and race. For each child, only the highest BLL was maintained in the data set. We coded timing (pre or post) of the BLL on the basis of the date of blood draw. We calculated age at time of blood draw.

We geocoded the data set with a dual range address locator, and manually con firmed accuracy of geocoded addresses. We conducted a series of spatial joins to assign participant records to Greater Flint munici palities and Flint wards (including those with high WLL), enabling the calculation of the number and percentage of children with EBLLs in each geographic region for both time periods. The reference value for EBLL was 5 μg/dL or greater. We identified Flint wards with high WLLs with water lead sampling maps.[38] Wards 5, 6, and 7 had the highest WLLs; in each ward, more than 25% of samples had a WLL higher than 15 ppb. We theorized that children living in this combination of wards would have the highest incidence of EBLLs (referred to as "high WLL Flint"; the remainder of Flint was referred to as "lower WLL Flint").

We derived overall neighborhood level socioeconomic disadvantage from census block group variables intended to measure material and social deprivation. We calculated these scores from an unweighted z score sum of rates of lone parenthood, poverty, low educational attainment, and unemployment (adapted from Pampalon et al.[39]; used pre viously in Flint by Sadler et al.[40]), and assigned these to each child on the basis of home address. Positive values denote higher disad vantage, and negative values denote lower disadvantage. Table 1 highlights the overall socioeconomic disadvantage score compari son by time period and area.

We created spatial references for EBLL risk and a predictive surface for BLL by using GIS, providing the ability to see otherwise invisible spatial–temporal patterns in envi ronmental exposure.[17] Because of the need to

TABLE 1—Demographic Comparison of the Time Periods Before (Pre) and After (Post) Water Source Change From Detroit-Supplied Lake Huron Water to the Flint River, by Area: Flint, MI, 2013 and 2015

	Outside Flint		All Flint		High WLL Flint		Lower WLL Flint	
Characteristic	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Gender, %								
Male	51.6	49.5	48.6	52.9	47.6	54.4	49.1	52.3
Female	48.4	50.5	51.4	47.1	52.4	45.6	50.9	47.7
Race/ethnicity, %								
African American	24.3	24.5	69.4	70.6	74.9	78.8	67.0	66.9
Other categories	75.7	75.5	30.6	29.4	25.1	21.2	33.0	33.1
Age, y, mean	1.89	1.83	2.09	2.06	2.06	2.02	2.11	2.07
Overall socioeconomic disadvantage score	−0.83	−0.98	2.94	2.88	2.18	2.39	3.28	3.10

Note. WLL = water lead level. No statistically significant differences were found in any pre post value within any of the 4 geographical areas.

understand spatial variations and geo graphically target resources, we also ran ordinary Kriging with a spherical semivario gram model on the entire data set for Greater Flint, allowing interpolation of associated BLL risks with lead in water. Previous methods for evaluating spatial variation in lead levels have ranged from multivariable analyses at the individual level[41] to in terpolation methods such as inverse distance weighting[42] and Kriging.[43] Given our as sumption that lead risk is spatially correlated in Greater Flint because of the age and condition of pipes, interpolation methods are appro priate for building a preliminary risk surface. Both inverse distance weighting and Kriging derive such surfaces by calculating values at unmeasured locations based on weighting nearby measured values more strongly than distant values.[44] Whereas inverse distance weighting is a deterministic procedure and relies on predetermined mathematical for mulae, Kriging has the added sophistication of using geostatistical models that consider spatial autocorrelation, thereby improving accuracy of prediction surfaces (ArcGIS Desktop version 10.3, Environmental Sys tems Research Institute, Redlands, CA). As well, Kriging can be run with relatively few input points: adequate ranges fall be tween 30 and 100 total points, although Kriging has been conducted with just 7.[44]

Our city of Flint sample included 736 children in the pre period and 737 children in the post period, which amounts to a density of approximately 22 points per square mile. Kriging has become an increasingly common method for measuring variations in soil lead, and is given more in depth treat ment elsewhere.[45] To examine change in proportion of children with EBLL from the pre to post time periods, we used χ^2 analysis with continuity correction for each area (outside Flint, all Flint, high WLL Flint, and lower WLL Flint). In addition, we ex amined differences in overall socioeconomic disadvantage scores from the pre to post time periods by using the independent *t* test. Finally, we used both χ^2 analysis with con tinuity correction and 1 way ANOVA to assess demographic differences by area. We used post hoc least significant difference analysis following statistically significant 1 way ANOVAs.

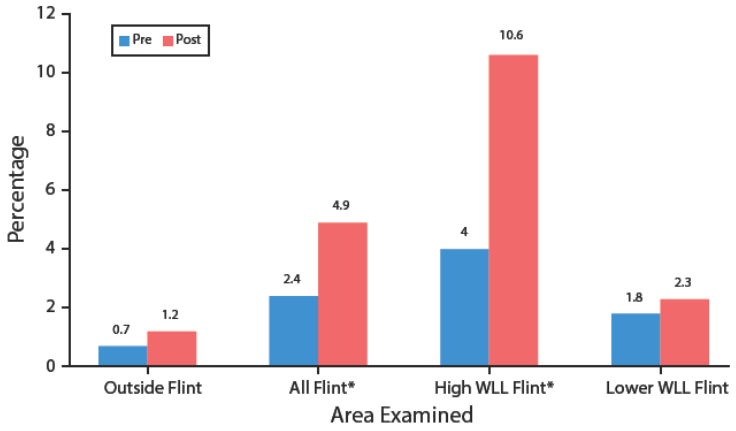
RESULTS

We uncovered a statistically significant increase in the proportion of Flint children with EBLL from the pre period to the pro portion of Flint children in the post period. In the pre period, 2.4% of children in Flint had an EBLL; in the post period, 4.9% of children had an EBLL ($P < .05$). By compar ison, outside of Flint water, the change in EBLL was not statistically significant (0.7% to 1.2%; $P > .05$). In high WLL Flint, EBLL increased from 4.0% to 10.6% ($P < .05$). Figure 1 shows the EBLL percentage change per area.

Results of the GIS analyses show signifi cant clustering of EBLLs within the Flint city limits. According to ordinary Kriging, Figure 2 shows a predicted surface based on observations of actual child BLL geocoded to home address to visualize BLL variation over space (measured in μg/dL). The darkest shades of red represent the highest risk for EBLL based on existing observations. Outside Flint, the entire county falls entirely within the lowest half of the range (in shades of blue); the only locations where predicted BLL is greater than 1.75 μg/dL is within Flint city limits.

Within Figure 2, each ward is also labeled according to the percentage of water samples that exceeded 15 ppb. The areas with the highest WLLs strongly coincide with the areas with the highest predicted BLLs. In addition, the high percentage of EBLL in wards 5, 6, and 7 also correspond with the high WLLs in wards 5, 6, and 7 (the labels in Figure 2). Table 2 shows ward specific WLLs, pre period and post period EBLL percentages, and predicted BLL and predicted change in BLL from Kriging.

Areas experiencing the highest predicted BLL in the post period (Figure 2) are generally also areas with greatest change in predicted BLL (measured in μg/dL) when compared with the pre period (Table 2; Figure A, available as a supplement to the online ver sion of this article at http://www.ajph.org). Figure A quantifies this rate of change with a green to red scale: large increases are shown in increasingly darker shades of red, whereas large decreases are shown in in creasingly darker shades of green. These once again match with city wards that ex perienced greater rates of EBLL percentage increase (Figure 1, Table 2). In wards 5 and 6 (which experienced a predicted 0.51 and 0.27 μg/dL increase, respectively), the EBLL percentage more than tripled. In ward 5, the EBLL percentage increased from 4.9% to 15.7% ($P < .05$). The area of intersection between wards 3, 4, and 5 (in the east side of the city) also appeared high in the Kriging analysis of Figure 2, and with a different unit of aggregation this neighborhood would also exhibit a significant increase in EBLL percentage. Ward 7 had high pre period and post period EBLL percentage levels above 5% (with a particularly high rate in the western portion of the ward). Citywide,



Note. WLL water lead level.
*$P < .05$.

FIGURE 1—Comparison of Elevated Blood Lead Level Percentage, Before (Pre) and After (Post) Water Source Change From Detroit-Supplied Lake Huron Water to the Flint River: Flint, MI, 2013 and 2015

4 wards (1, 4, 7, and 9) experienced decreases in predicted BLL, 3 wards (2, 5, and 6) experienced large increases, and 2 wards (3 and 8) remained largely the same (Figure A).

Overall, statistically significant differences exist between the areas examined (outside Flint, high WLL Flint, and lower WLL Flint) in all demographic characteristics except sex. The overall percentage of African American children is 24.4% outside Flint, compared with 76.8% in high WLL Flint and 67.0% in lower WLL Flint ($P < .001$). Children outside Flint were younger (mean = 1.86 years [SD = 1.10]) than high WLL Flint (mean = 2.04 years [SD = 1.02]) and lower WLL Flint (mean = 2.09 years [SD = 1.07]; $P < .001$). Differences in overall socioeconomic disadvantage scores are likewise significant ($P < .001$). Post hoc least significant difference analysis shows statistically significant differences for overall socioeconomic disadvantage between outside Flint and high WLL Flint ($P < .001$), between outside Flint and lower WLL Flint ($P < .001$), and between high WLL Flint and lower WLL Flint ($P < .001$).

DISCUSSION

Our findings reveal a striking increase in the percentage of Flint children with EBLL when we considered identical seasons before and after the water source switch, with no statistically significant increase in EBLL outside Flint. The spatial and statistical analyses highlight the greatest EBLL increase within certain wards of Flint, which correspond to the areas of elevated WLLs.

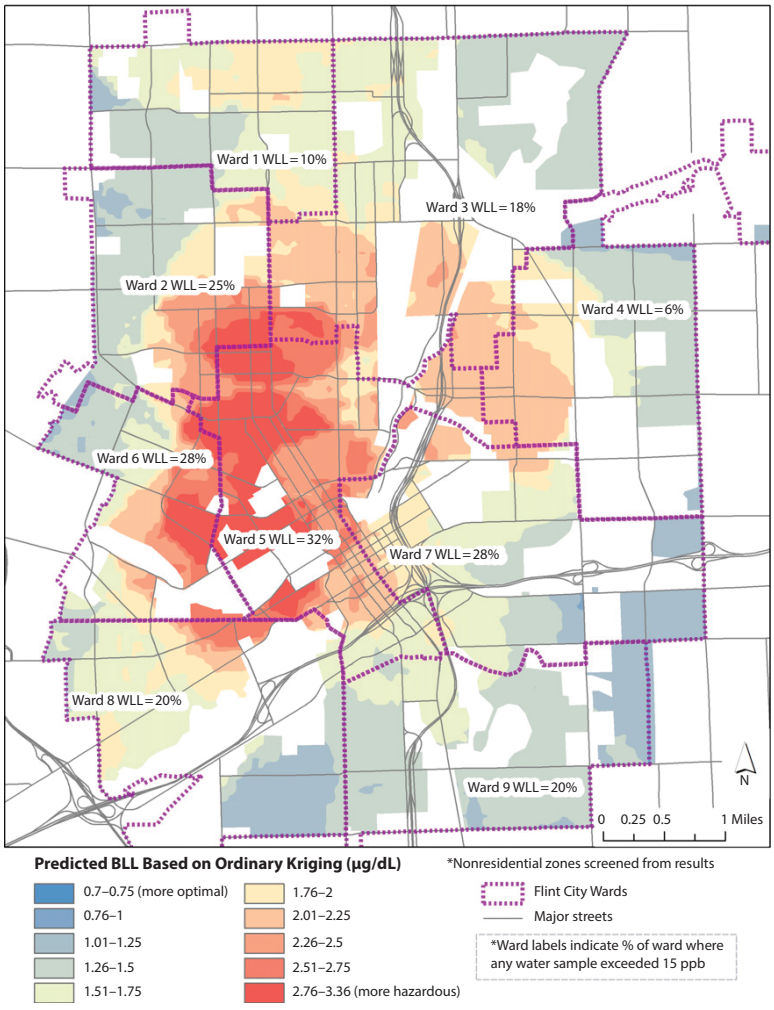
A review of alternative sources of lead exposure reveals no other potential environmental confounders during the same time period. Demolition projects by the Genesee County Land Bank Authority (Heidi Phaneuf, written communication, October 29, 2015) showed no spatial relationship to the areas of increased EBLL rates. As well, no known new lead producing factories nor changes in indoor lead remediation programs were implemented during the study period. Although Flint has a significant automobile history, the historical location of potentially lead using manufacturing (e.g., battery plants, paint and pigment storage, production plants) do not align with current exposures.

Because there was no known alternative source for increased lead exposure during this time period, the geospatial WLL results, the innate corrosive properties of Flint River water, and, most importantly, the lack of corrosion control, our findings strongly implicate the water source change as the probable cause for the dramatic increase in EBLL percentage.

As in many urban areas with high levels of socioeconomic disadvantage and minority populations,[46] we found a preexisting disparity in lead poisoning. In our pre water source switch data, the EBLL percentage in Flint was 2.4% compared with 0.7% outside Flint. This disparity widened with a post water source switch Flint EBLL of 4.8%, with no change in socioeconomic or demographic variables (Table 1). Flint children already suffer from risk factors that innately increase their lead exposure: poor nutrition, concentrated poverty, and older housing stock. With limited protective measures, such as low rates of breastfeeding,[47,48] and scarce resources for water alternatives, lead in water further exacerbates preexisting risk factors. Increased lead poisoning rates have profound implications for the life course potential of an entire cohort of Flint children already rattled with toxic stress contributors (e.g., poverty, violence, unemployment, food insecurity). This is particularly troublesome in light of recent findings of the epigenetic effects of lead exposure on one's grandchildren.[49]

The Kriging analysis showed the highest predicted BLLs within the city along a wide swath north and west of downtown. This area has seen significant demographic change, an increase in poverty, and an increase in vacant properties, especially over the past 25 years (Richard Sadler, written communication, October 5, 2015). Higher BLLs were also predicted northeast of downtown and in other older neighborhoods where poverty and vacancy rates have been high for many decades. Significantly, the biggest changes in predicted BLL since 2013 were also found in these impoverished neighborhoods; more stable neighborhoods in the far north and south of the city may have experienced improved predicted BLLs because of prevention efforts taken by the more often middle class residents in response to the water source change. Of considerable interest is that the areas shown as having the best public health indices by Board and Dunsmore in Figure 2 of their 1948 article[37] are virtually identical to the areas with the worst lead levels today.

After our preliminary zip code–based findings (pre to post water source switch



Note. BLL blood lead level; WLL water lead level.

FIGURE 2—Predicted Surface of Child Blood Lead Level and Ward-Specific Elevated Water Lead Level After (Post) Water Source Change From Detroit-Supplied Lake Huron Water to the Flint River: Flint, MI, 2015

EBLL = 2.1% to 4.0%; $P < .05$) were shared at a press conference,[50] the City of Flint and the Genesee County Health Department released health advisories,[51] and the county health department subsequently declared a public health emergency.[52] Shortly after, the State of Michigan released an action plan with short and long term solutions focusing on additional sampling, filter dis tribution, and corrosion control.[53] One week later, Michigan's governor revealed WLLs in 3 schools to be in the toxic range with 1 school showing a water lead level of 101 ppb, almost 7 times the level that requires remediation.[54] A $12 million plan to reconnect to Detroit's water source was announced.[54]

We undertook our current spatial analytic approach to overcome limitations of zip code boundaries and to develop a more thorough understanding of specific areas in Flint where EBLL risk is more severe (post office addresses often do not align with municipal boundaries in Michigan, and one third of Flint mailing addresses are not in the city of Flint). This spatial analysis is valuable for understanding subneighborhood patterns in EBLL risk because aggregation by zip code or ward minimizes the richness of spatial variation and creates artificial barriers that may obscure hot spots (as in the confluence of wards 3, 4, and 5).

Such use of spatial analysis for estimating lead exposure risk has been used to target blood lead–screening programs. In our case, in addition to identifying areas of risk, spatial analysis helps guide municipal and nongovernmental relief efforts aimed at identifying vulnerable populations in specific neighborhoods for priority distribution of resources (e.g., bottled water, filters, pre mixed formula).

Limitations

Our research contains a few limitations. First, we may have underestimated water based lead exposure. Our sample included all children younger than 5 years with blood lead screening, although the greatest risk from lead in water is in utero and during infancy when lead screening is not done. If lead screening were recommended at a younger age (e.g., 6 or 9 months) for children who live in homes with potential lead piping or lead service lines, more children with EBLL from water could be identified, although state and national comparison rates would be lacking. Second, lead screening is not completed for all children. It is mandated by Medicaid and CDC recommended for other high risk groups; such data may be skewed toward higher risk children and thus overestimate EBLL, especially in non–high risk areas. Third, the underserved population of Flint has significant housing instability: lead levels may reflect previous environmental expo sure, and exposure often cannot be ade quately estimated on the basis of current residence alone.[55]

Fourth, although large, our sample does not reflect all lead screening from Flint. We estimate that our data capture approxi mately 60% to 70% of the Michigan Child hood Lead Poisoning Prevention Program data for Flint. Annual data released from this program further support our findings, revealing an annual decrease in EBLL per centage from May to April 2010 to 2011 until the same period in 2013 to 2014 (4.1%,

TABLE 2—Ward-Based Comparison of WLL Percentages, Pre- and Post-Switch EBLL Percentages, and Predicted Post BLL and Change in Predicted BLL by Ordinary Kriging Geostatistical Analysis: Flint, MI, 2013 and 2015

Ward	WLL % > 15 ppb	Pre EBLL%	Post EBLL%	Predicted Post BLL[a]	Change in Predicted BLL From Pre to Post, µg/dL
1	10	0.0	2.8	1.4	−0.10
2	25	0.0	1.4	0.7	0.19
3	18	1.0	4.5	2.9	0.05
4	6	3.1	1.7	2.4	−0.15
5[b]	32	4.9	15.7	10.3	0.51
6[b]	28	2.2	9.3	5.5	0.27
7[b]	28	5.4	5.9	5.7	-0.26
8	20	2.7	1.4	2.0	0.01
9	20	3.4	1.6	2.5	−0.43

Note. BLL = blood lead level; EBLL = elevated blood lead level; WLL = water lead level.
[a]Ordinary Kriging geostatistical analysis.
[b]Indicates wards defined as high WLL risk in this study.

3.3%, 2.7%, 2.2%, respectively[56]; Robert L. Scott, e mail correspondence, September 25, 2015). Following the water switch in April 2014, the 4 year declining trend (as seen nationally) reversed with an annual EBLL of 3.0%.

We found consistent results (with control for age and methodology) when we analyzed Michigan Childhood Lead Poisoning Prevention Program data for both high WLL Flint (EBLL percentage increased: 6.6% to 9.6%) and outside Flint (EBLL percentage remained virtually unchanged: 2.2% to 2.3%). Our institution processed laboratory blood lead tests, however, had an even greater proportion of children with EBLLs versus state data in the post period. This may reflect that the BLLs processed at Hurley Medical Center, the region's only safety net public hospital, represent a patient population most at risk with limited resources to afford tap water alternatives.

Conclusions and Future Research

Future research directions include conducting more detailed geospatial analyses of lead service line locations with locations of elevated BLLs and WLLs; repeating identical spatial and statistical analyses in the same time period in 2016 reflecting changes associated with the health advisory and return to Lake Huron source water; analyzing feeding type (breastfed or reconstituted formula) for children with EBLLs; analyzing cord blood lead of Flint newborns compared with non Flint newborns; and conducting water lead testing from homes of children with EBLLs.

A once celebrated cost cutting move for an economically distressed city, the water source change has now wrought untold economic, population health, and geopolitical burdens. With unchecked lead exposure for more than 18 months, it is fortunate that the duration was not longer (as was the case in Washington, DC,'s lead in water issue).[16] Even so, the Flint drinking water crisis is a dramatic failure of primary prevention. The legal safeguards and regulating bodies designed to protect vulnerable populations from preventable lead exposure failed.

The Lead and Copper Rule requires water utilities to notify the state of a water source or treatment change recognizing that such changes can unintentionally have an impact on the system's corrosion control.[57] Although a review is required before implementing changes, the scope of risk assessment is not specified and is subject to misinterpretation. In response to the Flint drinking water crisis, the EPA recently released a memo reiterating and clarifying the need for states to conduct corrosion control reviews before implementing changes.[58] This recommendation is especially relevant for communities with aging infrastructures, usurped city governance, and minimal water utility capacity; in such situations, there is an increased need for state and federal expertise and oversight to support decisions that protect population health.

Through vigilant public health efforts, lead exposure has fallen dramatically over the past 30 years.[13] With the increasing recognition that no identifiable BLL is safe and without deleterious and irreversible health outcomes,[13] *Healthy People 2020* identified the elimination of EBLLs and underlying disparities in lead exposure as a goal.[59] Regrettably, our research reveals that the potentially increasing threat of lead in drinking water may dampen the significant strides in childhood lead prevention efforts. As our aging water infrastructures continue to decay, and as communities across the nation struggle with finances and water supply sources, the situation in Flint, Michigan, may be a harbinger for future safe drinking water challenges. Ironically, even when one is surrounded by the Great Lakes, safe drinking water is not a guarantee. AJPH

CONTRIBUTORS

M. Hanna-Attisha originated the study, developed methods, interpreted analysis, and contributed to the writing of the article. J. LaChance and R. Casey Sadler assisted with the development of the methods, analyzed results, interpreted the findings, and contributed to the writing of the article. A. Champney Schnepp assisted with the interpretation of the findings and contributed to the writing of the article.

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HUMAN PARTICIPANT PROTECTION

This study was reviewed and approved by Hurley Medical Center institutional review board.

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EXHIBIT 6

NTP | National Toxicology Program
U.S. Department of Health and Human Services

NTP Monograph

Health Effects of Low-Level Lead

June 2012

NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

June 13, 2012

Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

1.0 EXECUTIVE SUMMARY

1.1 Introduction

Lead (Pb) exposure remains a significant health concern despite policies and practices that have resulted in continued progress in reducing exposure and lowering blood Pb levels in the U.S. population. Pb is one of the most extensively studied environmental toxicants, with more than 28,900 publications on health effects and exposure in the peer-reviewed literature[1]. While the toxicity associated with exposure to high levels of Pb was recognized by the ancient Greeks and Romans, the adverse health effects associated with low-level Pb exposure became widely recognized only in the second half of the 20th century. Over the past 40 years, epidemiological studies, particularly in children, continue to provide evidence of health effects at lower and lower blood Pb levels. In response, the Centers for Disease Control and Prevention (CDC) has repeatedly lowered the concentration of Pb in blood that is considered "elevated" in children (from 30 µg/dL to 25 µg/dL in 1985 and to the current level of 10 µg/dL in 1991).

The purpose of this evaluation is to summarize the evidence in humans and to reach conclusions about whether health effects are associated with low-level Pb exposure as indicated by less than 10 micrograms of Pb per deciliter of blood (<10 µg/dL), with specific focus on the life stage (childhood, adulthood) associated with these health effects. This evaluation focuses on epidemiological evidence at blood Pb levels <10 µg/dL because health effects at higher blood Pb levels are well established such that the definition of an elevated blood Pb level is ≥10 µg/dL for both children and adults (ABLES 2009, CDC 2010a). Pb was nominated by the National Institute for Occupational Safety and Health for a National Toxicology Program (NTP) evaluation to assess the reproductive and developmental effects of Pb (see *http://ntp.niehs.nih.gov/mtg?date=20100510&meeting=BSC*). The scope of the evaluation has been expanded from the original nomination to include an evaluation of health effects other than reproduction and development (e.g., cardiovascular effects in adults) in order to maximize the utility of the evaluation.

[1] Based on an April 2012 PubMed search for keyword (MeSH) "lead" or "lead poisoning."

1.2 Methods

The key questions and general approach for developing the conclusions on the health effects of low-level Pb are outlined below. **Section 2.0** of this document contains additional details on the authoritative sources considered, the literature search strategy, and the peer-review process.

1.2.1 Key Questions

What is the evidence that adverse health effects are associated with blood Pb <10 µg/dL?

- What reproductive, developmental, neurological, immune, cardiovascular, and renal health effects are associated with blood Pb levels <10 µg/dL?
- What is the blood Pb level associated with a given health effect (i.e., <10 µg/dL or <5 µg/dL)?
- At which life stages (childhood or adulthood) is the effect identified?
- Are there data to evaluate the association between bone Pb and the health effect, and how does the association to this biomarker of Pb exposure compare to the association with blood Pb?

1.2.2 Approach to Develop Health Effects Conclusions

Conclusions in the NTP evaluation of Pb-related health effects in humans associated with low-level Pb were derived by evaluating the data from epidemiological studies with a focus on blood Pb levels <10 µg/dL. The evaluation includes a review of the primary epidemiological literature for evidence that low-level Pb is associated with neurological, immunological, cardiovascular, renal, and/or reproductive and developmental effects. These health effect areas were selected because there is a relatively large database of human studies in each area. The NTP considered four possible conclusions for specific health effects within each area:

Sufficient Evidence of an Association:
An association is observed between the exposure and health outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.

Limited Evidence of an Association:
An association is observed between the exposure and health outcome in studies in which chance, bias, and confounding could not be ruled out with reasonable confidence.

Inadequate Evidence of an Association:
The available studies are insufficient in quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between exposure and health outcome, or no data in humans are available.

Evidence of No Association:
Several adequate studies covering the full range of levels of exposure that humans are known to encounter (in this case limited to blood Pb levels <10 µg/dL) are mutually consistent in not showing an association between exposure to the agent and any studied endpoint.

The discussion of each health effect begins with a statement of the NTP's conclusion regarding whether the specific effect is associated with a blood Pb level <10 µg/dL or <5 µg/dL and the age group (childhood or adulthood) in which it is or is not identified, as well as the timing of exposure associated with the effect (prenatal, childhood, concurrent) if available. Then key data and principal studies considered in developing the NTP's conclusions are discussed in detail. General strengths and limitations of study designs were considered when developing conclusions, with prospective studies providing stronger evidence than cross-sectional or case-control studies. Each section concludes with a summary discussing each health effect, describing experimental animal data that relate to the human data, and stating the basis for the NTP conclusions.

For the purposes of this evaluation, "children" refers to individuals <18 years of age unless otherwise specified. In addition to the blood Pb level of <10 µg/dL, a lower effect level of <5 µg/dL was also selected because it is commonly used in epidemiological studies to categorize health effects data by exposure levels; therefore, data are often available to evaluate health effects for groups above and below this value as well.

1.2.3 Appendices of Studies Considered

The information to support the NTP's conclusions for individual health effects is presented in each chapter. In addition, human studies of groups with low-level Pb exposure that were considered in developing the conclusions are also abstracted for further reference and included in separate appendices for neurological effects, immune effects, cardiovascular effects, renal effects, and reproductive and developmental effects.

1.2.4 Authoritative Sources and Peer Review

In this evaluation, the NTP made extensive use of recent government assessments of the health effects of Pb, especially the U.S. Environmental Protection Agency (EPA) 2006 Air Quality Criteria Document (AQCD) for Lead (U.S. EPA 2006 and a draft updated version, 2012), which has undergone extensive external public peer review. In addition to the EPA's 2006 AQCD for Lead, sources include the Agency for Toxic Substances and Disease Registry's (ATSDR) 2007 Toxicological Profile for Lead (ATSDR 2007) and the CDC's Advisory Committee on Childhood Lead Poisoning Prevention reports, such as the 2010 Guidelines for the Identification and Management of Lead Exposure in Pregnant and Lactating Women (CDC 2010b).

The NTP used independent subject matter experts as technical advisers to provide scientific input and to review pre-public release drafts of each chapter summarizing the evidence that health effects are associated with low-level Pb, the appendices, and Section 3.0 that provides background on Pb exposure (see Contributors for a list of technical advisers). Peer review of the draft document was conducted by an expert panel of *ad hoc* reviewers at a public meeting held November 17-18, 2011, in Research Triangle Park, NC (see Peer-Review of the Draft NTP Monograph for details). Comments from peer reviewers and written public comments received on the draft monograph were considered during finalization of the document. The NTP concurred with the expert panel on all of the conclusions regarding health effects of Pb in this final document.

1.3 What Does It Mean to Refer to Blood Pb Levels <10 µg/dL?

The overwhelming majority of human epidemiological studies with Pb exposure data measured Pb in whole blood, and this measure of exposure serves as the basis for the evaluation of Pb levels <10 µg/dL. An individual's blood Pb level reflects an equilibrium between current environmental Pb exposure and the preexisting amount of Pb in the body, stored primarily in bone (Factor-Litvak *et al.* 1999, Brown *et al.* 2000, Chuang *et al.* 2001). In adults, bone and teeth store 90-95% of the total body burden of Pb, while in young children, bone Pb represents a smaller fraction (down to 70%) (Barry 1981, for review, see Barbosa *et al.* 2005, Hu *et al.* 2007). The body eliminates half of

the Pb in circulating blood (half-life) in approximately one month, while bone is a more stable repository for Pb and, therefore, bone Pb levels reflect cumulative exposure to Pb integrated over years or even decades (reviewed in Hu *et al.* 1998, Hu *et al.* 2007). The half-life of Pb in bone ranges from 10 to 30 years, depending on the rate of bone turnover, which in turn varies by type of bone and life stage (Rabinowitz 1991). In young children, continuous growth results in constant bone remodeling, and bone Pb is exchanged with blood Pb much more frequently than in adults (reviewed in Barbosa *et al.* 2005, Hu *et al.* 2007).

This evaluation focuses on the relationship between health effects and blood Pb levels because blood Pb is the most widely available measure of exposure, blood Pb reflects the equilibrium between current and past exposure, as described above, and numerous studies have reported an association between blood Pb levels and health outcomes. However, measuring Pb in one tissue at one point in time does not present a complete picture of either current or cumulative Pb exposure, and bone Pb reflects long-term stores of Pb in the body better than does blood Pb (reviewed in Barbosa *et al.* 2005, Hu *et al.* 2007); therefore, bone Pb data were also considered when available. Note that measuring bone Pb is expensive, requires specialized equipment that is not generally accessible, and requires study subjects to travel to the location of the measurement apparatus (K-x-ray fluorescence); thus, fewer Pb data are available for bone than for blood.

Before bans on Pb in paint, solder, and gasoline, environmental Pb levels in the United States were higher, so older adults accumulated more Pb as children than children do today. Average blood Pb levels in children 1-5 years of age have decreased 10-fold over the last 30 years, from 15.1 µg/dL in 1976-1980 to 1.51 µg/dL in 2007-2008 (geometric means; CDC 2007, 2011). This is clearly good news for current populations of children and represents a significant public health accomplishment. However, most U.S. adults who were born before 1980 had blood Pb levels >10 µg/dL during early childhood, so health effects in adults today may have been influenced by blood Pb levels >10 µg/dL that many individuals experienced earlier in life.

Keeping childhood blood Pb levels in mind, there are data on multiple health effects in adults for which studies report a significant relationship between concurrent blood Pb levels as adults and the health effect (e.g., elevated blood pressure, reduced kidney function, or decreases in specific measures of cognitive function). There is a considerable body of evidence that these health effects are associated with Pb exposure, and multiple studies report a significant association with concurrent blood Pb levels <10 µg/dL. Furthermore, the association with blood Pb is supported by the consistency of effects among epidemiological studies and biological coherence with animal data. It is well recognized that the role of early-life Pb exposure cannot be discriminated from the role of concurrent blood Pb without additional long-term studies. To eliminate the potential role of early-life blood Pb levels >10 µg/dL on health effects observed in adults with blood Pb levels <10 µg/dL, prospective studies (following a group over time) would be required in a group with blood Pb levels consistently <10 µg/dL from birth until measurement of the outcome of interest.

As described in **Section 1.2.2**, the NTP's conclusions were derived by evaluating data from epidemiological studies with a focus on blood Pb levels <10 µg/dL. The evidence discussed for specific health outcomes within each chapter varies by study design and type of analyses used to examine the relationship of the health outcome with blood Pb across the hundreds of studies evaluated. In some cases, studies examined only groups with blood Pb levels <10 µg/dL, <5 µg/dL, or even lower, and the association of the health effect with the blood Pb level is clear. For example, Lanphear *et al.* (2000) reported that higher blood Pb levels were associated with lower academic performance in a cross-sectional study (examining one point in time) of 4,853 children 6-16 years of age from the NHANES III data set. When they analyzed only children with blood Pb <10 µg/dL (n=4,681) or <5 µg/dL (n=4,043), the association with blood Pb was still significant ($p<0.001$ for <10 µg/dL and <5 µg/dL). In other cases, studies reported a significant association between blood Pb and an effect in a group whose mean blood Pb level was <10 µg/dL (e.g., higher blood Pb levels were associated with higher blood pressure in 964 adults in the Baltimore Memory Study (Martin *et al.* 2006)). These analyses support an effect of a blood Pb level <10 µg/dL, but they do not exclude the possibility that individuals significantly above or below the mean blood Pb level are driving the effect, or that past exposure levels are

driving the effect. Finally, some studies compared effects between two groups with higher and lower blood Pb levels. For example, Naicker *et al.* (2010) compared the effect of a blood Pb level ≥5 µg/dL with a blood Pb level <5 µg/dL on developmental markers of puberty in 13-year-old girls in South Africa (n=682) and found that a blood Pb level ≥5 µg/dL was significantly associated with delayed breast development, pubic hair development, and age of menarche.

1.4 Health Effects Evidence

1.4.1 NTP Conclusions

The NTP concludes that there is *sufficient* evidence for adverse health effects in children and adults at blood Pb levels <10 µg/dL, and <5 µg/dL as well (see Table 1.1 for summary of effect by life stage at which the effect is identified). A major strength of the evidence supporting effects of low-level Pb comes from the consistency demonstrated by adverse effects associated with blood Pb <10 µg/dL across a wide range of health outcomes, across major physiological systems from reproductive to renal, among multiple groups, from studies using substantially different methods and techniques, and for health effects in both children and adults.

In children, there is *sufficient* evidence that blood Pb levels <5 µg/dL are associated with increased diagnosis of attention-related behavioral problems, greater incidence of problem behaviors, and decreased cognitive performance as indicated by (1) lower academic achievement, (2) decreased intelligence quotient (IQ), and (3) reductions in specific cognitive measures. There is also *limited* evidence that blood Pb <5 µg/dL is associated with delayed puberty and decreased kidney function in children ≥12 years of age. There is *sufficient* evidence that blood Pb levels <10 µg/dL in children are associated with delayed puberty and reduced postnatal growth. There is *limited* evidence that blood Pb levels <10 µg/dL are associated with elevated serum immunoglobulin E (IgE), which is a principal mediator of hypersensitivity; consistent with this effect, there is *limited* evidence that blood Pb levels <10 µg/dL are associated with changes to an IgE-related health effect, allergy diagnosed by skin prick test to common allergens. There is *inadequate* evidence of an association between blood Pb <10 µg/dL in children and other allergic diseases, such as eczema or asthma. There is also *inadequate* evidence of an association between blood Pb <10 µg/dL and cardiovascular effects in children of any age, or renal function in children <12 years of age.

In adults, there is *sufficient* evidence that blood Pb levels <5 µg/dL are associated with decreased renal function and that blood Pb levels <10 µg/dL are associated with increased blood pressure and hypertension. There is *sufficient* evidence that maternal blood Pb levels <5 µg/dL are associated with reduced fetal growth and *limited* evidence that maternal blood Pb levels <10 µg/dL are associated with increased spontaneous abortion and preterm birth. There is *sufficient* evidence that blood Pb levels <10 µg/dL, and *limited* evidence that blood Pb levels <5 µg/dL, are associated with essential tremor in adults. There is also *limited* evidence for an association between blood Pb <10 µg/dL and increased cardiovascular-related mortality, decreased auditory function, the neurodegenerative disease amyotrophic lateral sclerosis (ALS), and decreases in specific measures of cognitive function in older adults. The NTP conclusions of associations between blood Pb levels <10 µg/dL in adults and health effects cannot completely eliminate the potential contributing effects of early-life blood Pb levels, as discussed in Section 1.3.

Although the relationship between many health effects and bone Pb as a measure of exposure has not been examined, the data support the importance of cumulative Pb exposure on cardiovascular effects of Pb in adults, as well as neurocognitive decline in adults, because the association between Pb and these endpoints is more consistent for bone Pb than for blood Pb.

1.4.2 Neurological Effects

The NTP concludes that there is *sufficient* evidence that blood Pb levels <5 µg/dL are associated with adverse neurological effects in children and *limited* evidence that blood Pb levels <10 µg/dL are associated with adverse neurological effects in adults (see Table 1.2 for summary of effects).

Unlike the data set for most other health effect areas, there are a number of prospective studies of neurological effects that include measures of prenatal exposure (either maternal blood or umbilical cord blood Pb levels). These prospective studies provide *limited* evidence that prenatal exposure to blood Pb levels <5 µg/dL is associated with decreases in measures of general and specific cognitive function

Table 1.1: NTP conclusions on health effects of low-level Pb by life stage

Life Stage	Blood Pb Level	NTP Conclusion	Principal Health Effects	Bone Pb Evidence
Children	<5 µg/dL	*Sufficient*	Decreased academic achievement, IQ, and specific cognitive measures; increased incidence of attention-related behaviors and problem behaviors	Tibia and dentin Pb are associated with attention-related behaviors, problem behaviors, and cognition.
		Limited	Delayed puberty and decreased kidney function in children ≥12 years of age	The one available study of bone Pb in children does not support an association with postnatal growth.
	<10 µg/dL	*Sufficient*	Delayed puberty, reduced postnatal growth, decreased IQ, and decreased hearing	No data
		Limited	Increased hypersensitivity/allergy by skin prick test to allergens and increased IgE* (not a health outcome)	No data
		Inadequate	*Any age* – asthma, eczema, nonallergy immune function, cardiovascular effects; *<12 years of age* – renal function	No data
Adults	<5 µg/dL	*Sufficient*	Decreased glomerular filtration rate; maternal blood Pb associated with reduced fetal growth	The one available study of bone Pb in the general population supports an association between bone Pb and decreased kidney function. Maternal bone Pb is associated with reduced fetal growth.
		Limited	Increased incidence of essential tremor	No data
	<10 µg/dL	*Sufficient*	Increased blood pressure, increased risk of hypertension, and increased incidence of essential tremor	The association between bone Pb and cardiovascular effects is more consistent than for blood Pb.
		Limited	Psychological effects, decreased cognitive function, decreased hearing, increased incidence of ALS, and increased cardiovascular-related mortality; maternal blood Pb associated with increased incidence of spontaneous abortion and preterm birth	The association between bone Pb and cognitive decline is more consistent than for blood Pb.
		Inadequate	Immune function, stillbirth, endocrine effects, birth defects, fertility or time to pregnancy**, sperm parameters**	No data

Abbreviations: ALS, amyotrophic lateral sclerosis; IgE, immunoglobulin E; IQ, intelligence quotient

*Increased serum IgE is associated with hypersensitivity; however, as described in **Section 1.4.3**, increased IgE does not equate to disease.

The NTP concludes that there is *inadequate* evidence that blood Pb levels <10 µg/dL are associated with fertility, time to pregnancy, and sperm parameters; however, given the basis of the original nomination, the NTP evaluated the evidence that higher blood Pb levels (i.e., >10 µg/dL) are associated with reproductive and developmental effects, and those conclusions are discussed in **Section 1.4.6 and presented in **Table 1.2**.

Table 1.2: NTP conclusions on health effects of low-level Pb by major health effect areas

Health Area	Population or Exposure Window		NTP Conclusion	Principal Health Effects	Blood Pb Evidence	Bone Pb Evidence
Neurological	Prenatal		*Limited*	Decrease in measures of cognitive function	Yes, <5 µg/dL	No data
			Limited	Decreased IQ, increased incidence of attention-related and problem behaviors, decreased hearing	Yes, <10 µg/dL	No data
	Children		*Sufficient*	Decreased academic achievement, IQ, and specific cognitive measures; increased incidence of attention-related and problem behaviors	Yes, <5 µg/dL	Tibia and dentin Pb are associated with attention, behavior, and cognition.
			Sufficient	Decreased hearing	Yes, <10 µg/dL	No data
	Adults		*Sufficient*	Increased incidence of essential tremor	Yes, <10 µg/dL	No data
			Limited	Psychiatric effects, decreased hearing, decreased cognitive function, increased incidence of ALS	Yes, <10 µg/dL	The association between bone Pb and cognitive decline is more consistent than blood.
			Limited	Increased incidence of essential tremor	Yes, <5 µg/dL	
Immune	Children		*Limited*	Increased hypersensitivity/allergy by skin prick test to common allergens and IgE* (not a health outcome)	Yes, <10 µg/dL	No data
			Inadequate	Asthma, eczema	Unclear	No data
	Adults		*Inadequate*	–	Unclear	No data
Cardiovascular	Children		*Inadequate*	–	Unclear	No data
	Adults		*Sufficient*	Increased blood pressure and increased risk of hypertension	Yes, <10 µg/dL	The association between bone Pb and cardiovascular effects is more consistent than blood.
			Limited	Increased cardiovascular-related mortality and ECG abnormalities	Yes, <10 µg/dL	
Renal	Children <12 years old		*Inadequate*	–	Unclear	No data
	Children ≥12 years old		*Limited*	Decreased glomerular filtration rate	Yes, <5 µg/dL	No data
	Adults		*Sufficient*	Decreased glomerular filtration rate	Yes, <5 µg/dL	Yes, one study
Reproductive and Developmental	Prenatal		*Limited*	Reduced postnatal growth	Yes, <10 µg/dL	No data
	Children		*Sufficient*	Delayed puberty, reduced postnatal growth	Yes, <10 µg/dL	One study does not support effects of bone Pb on growth.
			Limited	Delayed puberty	Yes, <5 µg/dL	
	Adults	Women	*Sufficient*	Reduced fetal growth	Yes, <5 µg/dL	Maternal tibia Pb is associated
			Limited	Increase in spontaneous abortion and preterm birth	Yes, <10 µg/dL	No data
		Men	*Sufficient*	Adverse changes in sperm parameters and increased time to pregnancy	Yes, ≥15-20 µg/dL	No data
			Limited	Decreased fertility	Yes, ≥10 µg/dL	No data
			Limited	Increased spontaneous abortion	Yes, >31 µg/dL	No data
		Adults	*Inadequate*	Stillbirth, endocrine effects, birth defects	Unclear	No data

Abbreviations: ALS, amyotrophic lateral sclerosis; ECG, electrocardiography; IgE, immunoglobulin E; IQ, intelligence quotient.
*Increased serum IgE is associated with hypersensitivity; however, as described in **Section 1.4.3**, increased IgE does not equate to disease.

evaluated in children. There is also *limited* evidence that prenatal exposure to blood Pb levels <10 µg/dL is associated with decreased IQ, increased incidence of attention-related behaviors and antisocial behavior problems, and decreased hearing measured in children. However, conclusions about effects of prenatal Pb exposure for outcomes evaluated as children are complicated by the high degree of correlation between prenatal and childhood blood Pb levels and as described below, blood Pb levels during childhood are also associated with these effects.

In children, there is *sufficient* evidence that blood Pb levels <5 µg/dL are associated with decreases in broad based and specific indices of cognitive function and an increase in attention-related behavioral problems and antisocial behavioral problems. The association between blood Pb and decreased IQ has been demonstrated in multiple prospective studies of children with blood Pb levels <10 µg/dL, pooled analyses that reported effects with peak blood Pb levels <7.5 µg/dL (Lanphear *et al.* 2005), and multiple cross-sectional studies that reported effects with mean blood Pb levels <5 µg/dL. Lower levels of academic achievement, as determined by class rank and achievement tests, have been reported in multiple prospective and cross-sectional studies of children with blood Pb <5 µg/dL. An association between blood Pb <5 µg/dL and decreases in specific measures of cognitive function has been demonstrated in prospective and cross-sectional studies using a wide range of tests to assess cognitive function. Increases in attention-related and problem behaviors are consistently reported in studies with mean blood Pb levels <5 µg/dL. The NTP concludes that blood Pb is associated with attention-related behaviors rather than attention deficit hyperactivity disorder (ADHD) alone because (1) this broad term more accurately reflects the range of Pb-associated behavioral effects in the area of attention, of which ADHD is one example on the more severe end of the spectrum, and (2) determination of ADHD in children from available studies are not as precise as an ADHD diagnosis by trained clinicians using specific *DSM-IV-TR* criteria. There is *sufficient* evidence that blood Pb levels <10 µg/dL in children are associated with decreased auditory acuity. Multiple cross-sectional studies reported hearing loss, as indicated by higher hearing thresholds and increased latency of brainstem auditory evoked potentials (BAEPs), in children with blood Pb levels <10 µg/dL.

In adults, there is *limited* evidence that blood Pb levels <10 µg/dL are associated with psychiatric outcomes (including anxiety and depression), decreased auditory function, ALS, and decreases in specific measures of cognitive function in older adults. There is *sufficient* evidence that blood Pb levels <10 µg/dL are associated with essential tremor in adults, and *limited* evidence for blood Pb levels <5 µg/dL. Associations with decreases in cognitive function in adults are more consistent for bone Pb than for blood Pb, suggesting a role for cumulative Pb exposure.

1.4.3 Immune Effects

The NTP concludes that there is *limited* evidence that blood Pb levels <10 µg/dL are associated with adverse immune effects in children and that there is *inadequate* evidence in adults (see **Table 1.2**).

In children, there is *limited* evidence that blood Pb levels <10 µg/dL are associated with changes to an immune-related health outcome such as allergy or increased hypersensitivity. There is also *limited* evidence that blood Pb levels <10 µg/dL are associated with elevated serum IgE levels. Five studies of groups with mean blood Pb levels of 10 µg/dL and below support the relationship between blood Pb and increased serum IgE. Two of these studies reported an association at blood Pb levels of ≥10 µg/dL rather than <10 µg/dL, and only one of the remaining studies adjusted for age, a particularly important confounder in analyses of IgE in children. Although increases in serum levels of total IgE are not definitive indicators of allergic disease, elevated levels of IgE are primary mediators of hypersensitivity associated with sensitization and allergic disease. Therefore, the studies demonstrating Pb-related increases in IgE suggest a link to hypersensitivity and support more definitive data such as a prospective study that found blood Pb levels <10 µg/dL were associated with increased hypersensitivity (or allergy by skin prick testing) in children. These data support the conclusion of *limited* evidence that increased hypersensitivity responses or allergy are associated with blood Pb levels <10 µg/dL in children; however, there is *inadequate* evidence of an association between blood Pb and other allergic diseases such as eczema or asthma.

There is *inadequate* evidence in adults to address the potential association between blood Pb <10 µg/dL and IgE, allergy, eczema, or asthma. Few studies have investigated the relationship between

immune function and Pb in humans, and most studies reported general observational markers of immunity rather than function. There is *inadequate* evidence that blood Pb levels <10 µg/dL are associated with observational immune effects such as altered lymphocyte counts or serum levels of IgG, IgM, or IgA in the blood of children or adults, because few studies have examined the lower exposure level and the available data are inconsistent. There is also *inadequate* evidence that blood Pb levels <10 µg/dL are associated with changes in immune function other than hypersensitivity, because few studies have examined immune function at lower blood Pb levels.

Bone Pb levels may be particularly relevant for cells of the immune system and immune function. All of the white blood cells or leukocytes that develop after birth are derived from progenitor cells in the bone marrow. Unfortunately, very few studies of immune effects have measured exposure other than blood Pb; therefore, the relative importance of blood or bone Pb levels for immune effects of Pb is unknown.

1.4.4 Cardiovascular Effects

The NTP concludes that there is *sufficient* evidence that blood Pb levels <10 µg/dL in adults are associated with adverse effects on cardiovascular function and that there is *inadequate* evidence to evaluate cardiovascular effects in children (see **Table 1.2** for summary of effects).

There is *sufficient* evidence of a bone Pb-related increase in the risk of hypertension and increases in blood pressure in adults. Two prospective studies and five cross-sectional studies support a significant association between bone Pb and blood pressure or hypertension in groups with blood Pb levels <10 µg/dL. Studies show less consistent associations between blood Pb and blood pressure or hypertension than for bone Pb; however, most of the recent studies with mean blood Pb levels <5 µg/dL found significant associations between concurrent blood Pb levels and increased blood pressure. There is *sufficient* evidence that blood Pb levels <10 µg/dL increase the risk of hypertension during pregnancy, supported by one prospective study and five cross-sectional studies with blood Pb levels during pregnancy <10 µg/dL. There is *limited* evidence of increased risk of cardiovascular mortality associated with blood Pb levels <10 µg/dL. An association between increased cardiovascular mortality and blood Pb is supported by three prospective studies (two of which used the same NHANES III sample) but is not supported by two other prospective studies. One of the studies that did not find an association with blood Pb (at a mean blood Pb level of 5.6 µg/dL) reported a significant association between bone Pb levels and increased cardiovascular mortality. There is *limited* evidence for Pb effects on other cardiovascular outcomes, including electrocardiography (ECG) abnormalities and clinical cardiovascular disease primarily due to lack of replication studies. Chronic Pb exposure appears to be more critical than current Pb exposure, as shown by more consistent associations between chronic cardiovascular effects and bone Pb than for blood Pb. Studies support an association with concurrent blood Pb levels; however, the potential effect of early-life blood Pb levels on cardiovascular outcomes in adults cannot be discriminated from the effect of concurrent blood Pb levels without additional prospective studies in a population for which blood Pb levels remain consistently below 10 µg/dL from birth until evaluation of the various cardiovascular outcomes as described in **Section 1.3**. There is *inadequate* evidence for Pb effects on heart rate variability, due to a lack of replicated studies.

There is *inadequate* evidence to assess whether children or menopausal women present a sensitive life stage for cardiovascular effects of Pb. No prospective studies have followed children with early-life Pb measures and evaluated cardiovascular health in adulthood. During periods of bone demineralization such as menopause and with osteoporosis, Pb stored in bone may enter the blood stream at a higher rate, increasing circulating Pb levels; for example, increased blood Pb levels have been demonstrated in women after menopause in several studies (e.g., Silbergeld *et al.* 1988, Symanski and Hertz-Picciotto 1995, Webber *et al.* 1995, Korrick *et al.* 2002). Too few studies have examined Pb-related cardiovascular health risks in postmenopausal women to enable conclusions.

Although hypertension can contribute to adverse renal effects, and kidney dysfunction can contribute to increased blood pressure, effects are considered separately in this evaluation because most studies examined one outcome or the other, rather than testing both systems comprehensively.

1.4.5 Renal Effects

The NTP concludes that there is *sufficient* evidence that blood Pb levels <5 µg/dL are associated with

adverse renal effects in adults (see Table 1.2 for summary of effects). There is *limited* evidence that blood Pb levels <5 µg/dL are associated with adverse renal effects in children ≥12 years of age, and the current evidence is inadequate to conclude that blood Pb <10 µg/dL is associated with renal effects in children <12 years of age.

There is *sufficient* evidence that blood Pb levels <5 µg/dL are associated with adverse effects on kidney function in adults. Most of the 13 epidemiological studies of the general population reported blood Pb levels <10 µg/dL are associated with (1) increased risk of chronic kidney disease (CKD), and (2) decreases in the estimated glomerular filtration rate (eGFR) and creatinine clearance, markers of kidney function. The associations are typically stronger in studies of groups with hypertension or diabetes. Few studies have examined other markers of Pb exposure, such as bone Pb; therefore, it is unknown whether blood or bone Pb levels would be a better measure of exposure for kidney effects related to Pb. Epidemiological data from the general population support an association with concurrent blood Pb levels in adults; however, the potential effect of early-life blood Pb levels on kidney function in adults cannot be discriminated from the effect of concurrent blood Pb levels without additional prospective studies in a group for which blood Pb levels remain consistently below 10 µg/dL from birth until evaluation of kidney function as described in Section 1.3.

There is *inadequate* evidence to address the potential association between blood Pb levels <10 µg/dL in children <12 years of age and impaired kidney function, because results are inconsistent and available studies of kidney function in young children are less reliable in general because tests of kidney function lack clear predictive value in this age group. There is *limited* evidence that blood Pb levels <5 µg/dL are associated with adverse effects on kidney function in children ≥12 years of age. This conclusion is based on one study of NHANES data, which reported effects in children ≥12 years of age that are consistent with reduced eGFR reported in adults in several NHANES studies.

1.4.6 Reproduction and Developmental Effects

The NTP concludes that there is *sufficient* evidence that blood Pb levels <10 µg/dL are associated with adverse health effects on development in children and that blood Pb levels <5 µg/dL are associated with adverse health effects on reproduction in adult women (see Table 1.2 for summary of effects).

Because most data on reproductive effects come from studies of occupational exposure, many of the available studies are for blood Pb levels >10 µg/dL. For this reason, and because the original nomination focused on reproductive and developmental effects, the evaluation of health effects in this area includes higher blood Pb levels, unlike other sections of this document. Consideration of these higher blood Pb levels resulted in several conclusions for Pb-related reproductive effects in men but did not affect the conclusions for women or children.

Unlike the data for most other health effect areas, a number of prospective studies of developmental effects have included prenatal measures of exposure (either maternal blood or umbilical cord blood). These prospective studies provide *limited* evidence that prenatal exposure to blood Pb levels <10 µg/dL is associated with reduced postnatal growth in children. Conclusions about effects of prenatal Pb exposure in children are complicated because blood Pb levels <10 µg/dL during childhood are also associated with reduced postnatal growth, and prenatal Pb levels are highly correlated with childhood Pb levels.

In children, there is *sufficient* evidence that blood Pb levels <10 µg/dL are associated with delayed puberty and *limited* evidence for this effect at blood Pb levels <5 µg/dL. Nine studies reported that concurrent blood Pb levels <10 µg/dL in children are associated with delayed puberty. There is *sufficient* evidence that blood Pb levels <10 µg/dL are associated with decreased postnatal growth. Numerous cross-sectional studies, including studies with large sample sizes such as the NHANES data sets, reported that concurrent blood Pb <10 µg/dL in children is associated with reduced head circumference, height, or other indicators of growth.

In adults, there is *sufficient* evidence that maternal blood Pb levels <5 µg/dL are associated with reduced fetal growth or lower birth weight. Three prospective studies with maternal blood Pb data during pregnancy, a large retrospective study (examining medical history) of >43,000 mother-infant pairs with a mean maternal blood Pb level of 2.1 µg/dL, and several cross-sectional studies of Pb levels in maternal or cord blood at delivery support an association

between higher blood Pb and reduced fetal growth at mean blood Pb levels from 1 to 10 µg/dL. Although maternal or paternal bone Pb data are not available in most studies of reproductive health outcomes, a set of studies of a single group reported that higher maternal bone Pb is related to lower fetal growth. There is also *limited* evidence that maternal blood Pb levels <10 µg/dL are associated with preterm birth and spontaneous abortion. Although several prospective studies reported an association between maternal blood Pb and preterm birth, the conclusion of *limited* evidence is due to inconsistent results and a retrospective study with a large cohort of >43,000 mother-infant pairs not finding an association between maternal blood Pb levels and preterm birth. The conclusion of *limited* evidence for an association with spontaneous abortion is based primarily on the strength of a single prospective nested case-control study in women, with additional support provided by occupational studies that reported an association with Pb exposure but lacked blood Pb measurements. In men, there is *inadequate* evidence that blood Pb levels <10 µg/dL are associated with effects on reproduction.

In men there is *sufficient* evidence that blood Pb levels ≥15 µg/dL are associated with adverse effects on sperm or semen and that blood Pb levels ≥20 µg/dL are associated with delayed conception time. Decreases in sperm count, density, and concentration have been reported in multiple retrospective and cross-sectional occupational studies of men with mean blood Pb levels from 15 to 68 µg/dL. Four studies reported increased time to pregnancy in women whose male partners had blood Pb levels of 20-40 µg/dL. A single retrospective occupational study reported increased risk of infertility among men with blood Pb levels ≥10 µg/dL, and the consistency of this observation with other studies reporting effects on time to pregnancy at higher blood Pb levels supports a conclusion of *limited* evidence that blood Pb levels ≥10 µg/dL in men are associated with other measures of reduced fertility. There is also *limited* evidence that paternal blood Pb levels >31 µg/dL are associated with spontaneous abortion, based primarily on the strength of a single retrospective nested case-control study in men, with additional support provided by occupational studies that reported an association with Pb exposure but lacked blood Pb measurements.

1.5 Future Research

There are robust data and *sufficient* evidence that blood Pb levels <10 µg/dL in children and adults are associated with adverse health effects across a wide range of health outcomes, as described above. Over time, epidemiological studies have provided data to support health effects at lower and lower blood Pb levels, particularly in children. Prospective studies in children better address the lower limits of Pb exposure associated with health effects because they focus on children whose blood Pb levels remain <10 µg/dL or <5 µg/dL with certainty throughout their lifetime. Studies of health effects in adults cannot eliminate the potential effects of early-life blood Pb levels on health effects observed as adults. This is particularly important in an evaluation of the health effects of blood Pb levels <10 µg/dL because older adults were likely to have had blood Pb levels >10 µg/dL as children (see discussion in Section 1.3), compared with only 0.8% of children with confirmed blood Pb levels >10 µg/dL in 2008.

Clarification of the effects of early-life blood Pb levels relative to the effects of concurrent blood Pb levels remains a significant issue for evaluating Pb-related health effects in adults. Epidemiological data from adults support an association between concurrent blood Pb levels <5 µg/dL and decreased renal function and between concurrent blood Pb levels <10 µg/dL and increased blood pressure and hypertension. Future research should be directed at clarifying the extent to which early life exposure (e.g., blood Pb levels >10 µg/dL) contribute to health effects observed in adults. Long-term prospective studies in a group for which blood Pb levels remain consistently <10 µg/dL from birth until the outcome of interest is measured would take one step in this direction by eliminating the potential role of early-life blood Pb levels >10 µg/dL on health effects observed in adults with concurrent blood Pb levels <10 µg/dL.

2.0 METHODS

The NTP's conclusions on health effects of low-level Pb are based on evaluation of data from epidemiological studies with a focus on blood Pb levels <10 µg/dL. The methodological approach began with a statement of the key questions addressed by this evaluation. The general approach for developing the NTP's conclusions on evidence of an association between blood Pb levels <10 µg/dL and specific health effects is described below, along with the format and definitions used throughout the document. The structure of appendix tables summarizing the relevant literature for each health effect area is also described below. The NTP considered several recent government evaluations of the health effects of Pb as authoritative sources to supplement a review of the primary epidemiological literature, and these documents are briefly described in this section. The NTP also used independent subject matter experts as technical advisors to provide scientific input and to review pre-public release drafts of each chapter summarizing the evidence for health effects associated with low-level Pb, as well as the appendices and background exposure section. The literature search strategy and details of the peer-review process are also described below.

2.1 Key Questions

What is the evidence that adverse health effects are associated with blood Pb <10 µg/dL?

- What reproductive, developmental, neurological, immune, cardiovascular, and renal health effects are associated with blood Pb levels <10 µg/dL?
- What is the blood Pb level associated with a given health effect (i.e., <10 µg/dL or <5 µg/dL)?
- At which life stages (childhood or adulthood) is the effect identified?
- Are there data to evaluate the association between bone Pb and the health effect, and how does the association to this biomarker of Pb exposure compare to the association with blood Pb?

2.2 Approach to Develop Health Effects Conclusions

Conclusions in the NTP evaluation of Pb-related health effects in humans associated with low-level Pb were derived by evaluating the data from epidemiological studies with a focus on blood Pb levels <10 µg/dL. The evaluation includes a review of the primary epidemiological literature, and these studies formed the basis for the NTP conclusions. The quality of individual studies was considered in reaching health effects conclusions, including consideration of known confounders, appropriateness of the method of diagnosis, strength of the study design, and the sample size. General strengths and limitations of study designs were considered when developing conclusions, with prospective studies providing stronger evidence than cross-sectional or case-control studies. Consistency of effects across the body of evidence and important factors such as the number of studies, exposure levels, biological plausibility, and support from the animal literature were all assessed when developing the NTP conclusions.

Draft NTP conclusions were evaluated for consistency with health effect conclusions from recent government evaluations considered authoritative sources: the U.S. EPA 2006 Air Quality Criteria Document (AQCD) for Lead (U.S. EPA 2006) and the ATSDR 2007 Toxicological Profile for Lead (ATSDR 2007) (see **Section 2.4** for discussion). Technical advisors with relevant subject matter expertise served as another authoritative source (see **Section 2.4.4** for details). Technical advisors were asked to critically evaluate every one of the NTP's conclusions regarding the potential for adverse health effects to occur at blood Pb levels <10 µg/dL and to determine whether the science cited was technically correct, clearly stated, and supported the NTP's conclusions in pre-public release drafts of each chapter addressing specific health effect areas. As described in **Section 2.6** and **Peer-Review of the Draft NTP Monograph,** a draft version of the Monograph was released for public comment and peer review by an expert panel of ad hoc reviewers. Written public comments and comments from peer reviewers were considered during finalization of the document.

Studies were evaluated for evidence that low-level Pb is associated with neurological, immunological, cardiovascular, renal, and/or reproductive and developmental effects. These health effects areas were selected because there is a relatively large database of human studies in each area. The NTP considered four possible conclusions for specific health effects within each area.

Sufficient Evidence of an Association:

An association is observed between the exposure and health outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.

Limited Evidence of an Association:
An association is observed between the exposure and health outcome in studies in which chance, bias, and confounding could not be ruled out with reasonable confidence.

Inadequate Evidence of an Association:
The available studies are insufficient in quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between exposure and health outcome, or no data in humans are available.

Evidence of No Association:
Several adequate studies covering the full range of levels of exposure that humans are known to encounter (in this case limited to blood Pb levels <10 µg/dL) are mutually consistent in not showing an association between exposure to the agent and any studied endpoint.

The discussion of each health effect begins with a statement of the NTP's conclusion regarding whether the specific effect is associated with a blood Pb level <10 µg/dL or <5 µg/dL and the age group in which it is or is not identified (childhood or adulthood), as well as the timing of exposure associated with the effect (prenatal, childhood, concurrent) when available. Then key data and principal studies considered in developing the NTP's conclusions are then discussed in detail. Each section concludes with a summary discussing each health effect, describing experimental animal data that relate to the human data, and stating the basis for the NTP's conclusions.

For the purposes of this evaluation, "children" refers to individuals <18 years of age unless otherwise specified. In addition to the blood Pb level of <10 µg/dL, a lower effect level of <5 µg/dL was also selected because it is commonly used in epidemiological studies to categorize health effect data by exposure levels; therefore, data are often available to evaluate health effects for groups above and below this value as well. Findings described in the text as having an "association" or "significant association" reflect a statistically significant result with a p-value <0.05 unless otherwise indicated.

2.3 Appendices of Studies Considered

The information to support the NTP's conclusions for individual health effects is presented in each chapter. Human studies from groups with low-level Pb exposure that were considered in developing the conclusions are also abstracted for further reference and are included in separate appendices for each health effect area.

Each appendix table includes the following column headings:

Description: study design, reference, and geographic location
Population: sample size, description, years of study, and percent male
Age: mean age and standard deviation of the subjects
Blood Pb: mean blood Pb level and standard deviation (in µg/dL)
Outcomes: health effects assessed
Statistical: methods used and cofactors included in analyses
Findings: summary of results (bolded if statistical significance tests had a p-value <0.05)
Observed Effect: conclusion (Effect/No Effect/Equivocal) and description

Potential overlap of subjects in multiple publications from the same epidemiological study is indicated in the first column of each appendix. These studies were not considered as independent findings to be evaluated in developing the NTP's conclusions.

The grouping of studies within each appendix table varied by health effects considered:

Appendix A. Neurological Effects: no grouping, meta-analyses shaded
Appendix B. Immune Effects: grouped by low (<15 µg/dL) and high (>15 µg/dL) exposure
Appendix C. Cardiovascular Effects: grouped by outcome, meta-analyses shaded
Appendix D. Renal Effects: no grouping
Appendix E. Reproductive and Developmental Effects: grouped by outcome

Within each grouping, studies are listed alphabetically by first author and then chronologically by publication date. For the appendix tables grouped by outcome, if a publication contained results that applied to more than one group, results specific to each outcome group were included.

The NTP's conclusions are based on the evidence from human studies with blood Pb levels of <10 µg/dL and therefore the abstracted studies in

the appendices are mainly those with a mean blood Pb level of <10 µg/dL. However, studies with data reflecting mean exposure levels up to 15 µg/dL were also included so that effects at and around 10 µg/dL were not missed during the evaluation. Reproductive effects in studies with mean blood Pb levels >15 µg/dL were included in the evaluation because the data set of human studies on these effects associated with lower blood Pb levels is limited. For this reason, and because the original nomination focused on reproductive and developmental effects, the evaluation of health effects in this area includes higher blood Pb levels. The immunological effects database was adequate to make conclusions on several effects at blood Pb levels <10 µg/dL; however, because the NTP makes limited reference to studies in humans at higher blood Pb levels, Appendix B also includes human studies with higher blood Pb levels (i.e., >15 µg/dL).

2.4 Authoritative Sources Considered

Recent government evaluations of the health effects of Pb include the U.S. EPA 2006 AQCD for Lead (U.S. EPA 2006), the ATSDR 2007 Toxicological Profile for Lead (ATSDR 2007), and the CDC's Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) Reports, such as the 2010 Guidelines for the Identification and Management of Lead Exposure in Pregnant and Lactating Women (CDC 2010). The NTP made extensive use of these evaluations in its assessment, especially the EPA's 2006 AQCD for Lead (U.S. EPA 2006) because it underwent extensive external public peer review. NTP considered the conclusions and data summaries from the EPA and ATSDR documents. In general, NTP concurred with the conclusions and agreed that the data support them. Differences between the NTP's conclusions and the 2007 ATSDR Toxicological Profile for Lead (ATSDR 2007) and the EPA's 2006 AQCD (U.S. EPA 2006) are identified for specific endpoints in this document. The database of studies on health effects in humans is supported by an equally large body of experimental animal studies. In this document, the experimental animal data are considered when relevant to reaching conclusions primarily based on the human literature. The reader is referred to the U.S. EPA AQCD for Lead (U.S. EPA 2006) and ATSDR Toxicological Profile for Lead (ATSDR 2007) for more in-depth reviews of the animal data.

2.4.1 U.S. EPA 2006 Air Quality Criteria Document (AQCD) for Lead

The EPA's AQCD is an exhaustive review and assessment (>1,200 pages with an additional 900 pages of tables and other annex material) of the scientific information related to human health and ecological effects associated with Pb in ambient air (U.S. EPA 2006). The EPA's AQCDs are published periodically (the latest draft document, released February of 2012, updates the review with literature published since the U.S. EPA 2006 AQCD for Lead (U.S. EPA 2006)) to provide key scientific assessment of evidence to support periodic review of the current Pb National Ambient Air Quality Standards. The 2006 EPA AQCD for Lead (U.S. EPA 2006) is an extensively reviewed document that was subject to public comment and review by the Clean Air Scientific Advisory Committee in a series of public meetings. Because EPA is in the process of revising the AQCD, the 2012 Integrated Science Assessment for Lead (U.S. EPA 2012) is available only as a draft at this time.

2.4.2 ATSDR 2007 Toxicological Profile for Lead

The 2007 Toxicological Profile for Lead (ATSDR 2007) is a comprehensive evaluation of the available toxicological and epidemiological data on Pb. The toxicological profile is organized around a public health statement summarizing the toxicological and adverse health effects for Pb. ATSDR's peer-review process for their toxicological profiles includes release for public comment and a peer review by a panel of experts.

2.4.3 CDC Lead Panel Documents

CDC's fifth revision of the statement on preventing Pb poisoning in young children includes a companion document developed by the ACCLPP that reviews the scientific evidence for adverse health effects in children at blood Pb levels <10 µg/dL. The committee concluded that the "overall weight of the evidence supports an inverse (negative) association between BLLs [blood lead levels] <10 µg/dL and the cognitive function in children" (CDC 2005). The report focuses primarily on cognitive function, but the committee also concluded that additional health effects (e.g., other neurological functions, stature, sexual maturation) were associated with blood Pb levels <10 µg/dL in children.

The ACCLPP has also prepared a draft report providing Guidelines for the Identification and

Management of Lead Exposure in Pregnant and Lactating Women (CDC 2010). The report provides "practical considerations regarding preventing lead exposure during pregnancy, assessment and blood lead testing during pregnancy, medical and environmental management to reduce fetal exposure, breastfeeding and follow-up of infants and children exposed to lead in utero." The document summarizes the evidence from human studies through 2008 for health effects of Pb in pregnant women and the developing child (concentrating on exposure during gestation and from breastfeeding) and provides guidance for clinicians.

2.4.4 Technical Advisors

The primary mechanism for obtaining scientific input during development of the draft NTP Monograph on Health Effects of Low-Level Pb was through technical advisors (see **Contributors** for list of technical advisors). Technical advisors with relevant subject matter expertise were asked to provide input on issues of scientific complexity, adequacy of the literature review, and overall presentation of a pre-public release version of the draft NTP monograph. These advisors critically evaluated each of the NTP's health effects conclusions and the basis for those conclusions, as well as the appendices and the background exposure section. Individuals who served as technical advisors were screened for potential conflict of interest.

2.5 Literature Search Strategy

The 2006 EPA AQCD for Lead (U.S. EPA 2006) and the 2007 ATSDR Toxicological Profile for Lead (ATSDR 2007) were screened for citations on health effects assessed at low-level Pb exposure. The NTP's conclusions are based on the evidence from human studies with blood Pb levels of <10 µg/dL with data reflecting mean exposure levels up to 15 µg/dL also considered so that effects at and around 10 µg/dL were not missed during the evaluation. Primary literature searches in MEDLINE®, Web of Science, Scopus, Embase, and TOXNET were conducted on March 1-5, 2010, to identify relevant studies published subsequent to the 2006 EPA and 2007 ATSDR documents. Search terms included the following MeSH subject headings: lead or lead poisoning; "diseases category" or "anatomy category" for health effects; and humans[mh or Medical Subject Headings in MEDLINE] or epidemiology[sh or SubHeadings in MEDLINE] or epidemiologic studies[mh] or age groups[mh] for limiting to human studies.

Because of the heteronym nature of the term "lead," text word searching used four approaches: (1) searched for "lead" in title; (2) used various combinations to focus on low-level exposure: "low lead" or "low blood lead" or "lower lead" or "lower blood lead" or "low level" or "low levels" or "lower level" or "lower levels" or "lead level" or "lead levels" or "low dose" or "lead induced" or "lead intake" or "blood lead"; (3) combined "lead" with heavy metals or cadmium or mercury or arsenic; and (4) when necessary, excluded "lead to" or "leads to" from search results. For databases that allowed proximity searching, "lead" and "low or lower" were required to be in the same sentence. This strategy would retrieve articles such as "low cadmium and lead levels" or "low blood and urine lead levels" or "lower concentrations of lead in the blood." Text words used to retrieve human studies included human(s), resident(s), inhabitant(s), population, people, subject(s), patient(s), case(s), women, men, girls, boys, parent(s), mother(s), father(s), adult(s), child, children, childhood, adolescent(s), infant(s), toddler(s), newborn(s), occupation(al), work, workplace, worker(s), employee(s), laborer(s), and staff.

An updated search was performed September 12-15, 2011, to identify any additional references published since the last search. Technical advisors who were involved in the review of the draft document (see below) were also asked to identify relevant studies. In addition, NTP published a Federal Register notice regarding the low-level Pb evaluation, inviting submission of information about recently published/in-press studies that might be relevant for consideration in the evaluation (75 FR 51815).

2.6 Peer-Review Process

Peer review of the Draft NTP Monograph was conducted by an expert panel of ad hoc reviewers with relevant scientific background (i.e., expertise in Pb or metals related to reproductive and developmental toxicology, neurotoxicology, immunotoxicology, cardiovascular toxicology, renal toxicology, and exposure) at a public meeting held November 17-18, 2011 in Research Triangle Park, NC (see **Peer Review of the Draft NTP Monograph** for list of panel members). The selection of panel members and conduct of the peer review were performed in accordance with the

Federal Advisory Committee Act and Federal policies and regulations. The panel was charged to determine whether the science cited in the draft NTP Monograph on Low-Level Lead was technically correct, was clearly stated, and supported NTP's conclusions regarding the potential for adverse health effects to occur at blood Pb levels <10 µg/dL. Public comments received as part of the NTP's evaluation of health effects of low-level Pb, meeting minutes, and other materials from the peer-review meeting are available at *http://ntp.niehs.nih.gov/go/37090.* Written public comments and comments from peer reviewers were considered during finalization of the document.

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3.0 EXPOSURE

Studies of health effects of Pb in humans commonly use one of several biomarkers to reflect the level of Pb exposure in an individual. The overwhelming majority of studies measure whole-blood Pb because blood samples are routinely collected and stored in large epidemiological studies; furthermore, the methods for measuring Pb in whole blood are widespread and extensively validated. Bone Pb is more likely to reflect cumulative exposure but must be measured by specialized equipment and requires measurements to be made on subjects present at a research clinic. Measures of Pb in urine and hair have been used in some studies, but how well they reflect the body burden of Pb is less clear.

Pb is ubiquitous in the environment, but the level of exposure to Pb that individuals experience can vary and depends on many factors, including occupation, geography, and life stage. This chapter briefly discusses common routes of exposure to Pb and associated factors that may affect the risk of exposure.

The NTP made extensive use of recent government evaluations of Pb exposure and associated health effects in developing the current assessment. The EPA's 2006 AQCD for Lead (U.S. EPA 2006) and ATSDR's Toxicological Profile for Lead (ATSDR 2007) both contain extensive review and discussion of Pb exposure, with the AQCD document particularly focusing on Pb in air. The NTP also used two CDC documents focused on particularly vulnerable groups: the 2010 Guidelines for the Identification and Management of Lead Exposure in Pregnant and Lactating Women and the 2005 Preventing Lead Poisoning in Young Children report (CDC 2005b, 2010). The EPA is in the process of revising the AQCD and has released an external review draft that also includes extensive discussion of Pb exposures (U.S. EPA 2012).

3.1 What Does It Mean to Refer to Blood Pb <10 µg/dL?

This evaluation focuses on the relationship between health effects and blood Pb levels <10 µg/dL because (1) whole-blood Pb is the most widely available measure of exposure, (2) blood Pb reflects an equilibrium between current environmental Pb exposures and Pb stored in bone from prior exposures, and (3) numerous studies have reported an association between blood Pb levels and health effects.

However, measuring Pb in one tissue at one point in time does not present a complete picture of either current or cumulative Pb exposure. Bone Pb is considered superior to blood Pb in reflecting the long-term stores of Pb in the body (e.g., Rabinowitz 1991, reviewed in Barbosa *et al.* 2005, Hu *et al.* 2007). When available, bone Pb data were also considered in this evaluation. However, measuring bone Pb is expensive and requires subjects to travel the location of the specialized measurement apparatus (K-x-ray fluorescence). A number of authors have hypothesized that blood Pb may provide a better measure of Pb exposure in children or other subjects with active bone remodeling (see reviews by Barbosa *et al.* 2005, Hu *et al.* 2007). However, few studies in children have examined the usefulness of bone Pb data as a measure of exposure in children to test this hypothesis, other than studies that reported Pb levels in shed deciduous teeth (baby teeth).

When data were available for multiple measures of exposure, the association between health effects and either blood Pb or bone Pb levels was evaluated in this document. While the vast majority of exposure data were in the form of blood Pb measurements, in some cases there was enough data to begin to compare the association between a given health effect for both blood Pb and bone Pb levels. For example, bone Pb in adults appears to be more consistent than blood Pb in its relationship to decreases in specific cognitive measures (specifically in older adults), hypertension, and other cardiovascular effects. Although the relative strength of the association between measures of exposure and the health outcome has not been widely examined, in some cases bone and blood Pb measurements are available in the same group or study and the data have been analyzed in a method that allows such a comparison. For example, multiple studies have reported that blood Pb levels were associated with decreased IQ in the Yugoslavia Prospective Study (see discussion in **Section 4.3.1**). Wasserman *et al.* (2003) demonstrated a stronger association between bone Pb and IQ than for blood in a subset analysis of 167 children with blood and bone Pb measurements. In fact, the association with tibia bone Pb remained significant in a statistical model that controlled for concurrent or average lifetime blood Pb levels.

Pb exposures in the United States have dramatically declined over the last 30 years after bans on Pb in paint, solder, and gasoline, representing a significant

public health accomplishment and protection for current populations of children. However, children born in the United States in the 1970s had a mean blood Pb of 15 µg/dL during early childhood. Consequently, health effects in adults today may have been influenced by blood Pb levels >10 µg/dL that many individuals experienced earlier in life.

Keeping these childhood blood Pb levels in mind, there are data on multiple health effects in adults for which studies report a significant relationship with concurrent blood Pb levels (e.g., elevated blood pressure, reduced kidney function, or decreases in specific measures of cognitive function). There is a considerable body of evidence that these health effects are associated with Pb exposure, and multiple studies report a significant association with concurrent blood Pb levels <10 µg/dL. Furthermore the association with blood Pb is supported by the consistency of effects across epidemiological studies, as well as biological coherence with animal data. It is well recognized that the role of early-life Pb exposure cannot be discriminated from the role of concurrent blood Pb without additional long-term studies.

As described in **Section 2.2**, the NTP's conclusions were derived by evaluating data from epidemiological studies with a focus on blood Pb levels <10 µg/dL. The evidence discussed for specific health outcomes within each chapter varies by study design and type of analyses used to examine the relationship of the health outcome with blood Pb across the hundreds of studies evaluated. In some cases, studies examined only groups with blood Pb levels <10 µg/dL, <5 µg/dL, or even lower, and the association of the health effect with the blood Pb level is clear. For example, Lanphear *et al.* (2000) reported that higher blood Pb was associated with lower academic performance in a cross-sectional study of 4,853 children ages 6-16 from the NHANES III data set. When they analyzed only children with blood Pb <10 µg/dL (n=4,681) or <5 µg/dL (n=4,043), the association with blood Pb was still significant ($p<0.001$ for <10 µg/dL and <5 µg/dL). In other cases, studies reported a significant association between blood Pb and an effect in a group whose mean blood Pb level <10 µg/dL (e.g., higher blood Pb level was associated with higher blood pressure in a study of 964 adults in the Baltimore Memory Study (Martin *et al.* 2006)). These analyses support an effect of a blood Pb level <10 µg/dL, but they do not exclude the possibility that individuals significantly above or below the mean blood Pb level are driving the effect, or that past exposure levels are driving the effect. Finally, some studies compared effects between two groups with higher and lower blood Pb levels. For example, Naicker *et al.* (2010) compared the effect of a blood Pb level ≥5 µg/dL with a blood Pb level <5 µg/dL on developmental markers of puberty in 13-year-old girls in South Africa (n=682) and found that blood Pb ≥5 µg/dL was significantly associated with delayed breast development, pubic hair development, and age of menarche.

3.2 Biomarkers of Pb Exposure

The large majority of human epidemiological studies that report individual Pb exposure levels measured Pb in blood samples. This chapter discusses U.S. blood Pb levels and trends for age, gender, and race or ethnicity. Bone Pb has been measured in some studies and is considered to more accurately reflect cumulative body burden of Pb because of the longer half-life of Pb in bone than in blood (reviewed in Barbosa *et al.* 2005, Hu *et al.* 2007). Bone and blood Pb are currently the most useful tools for measuring the body burden of Pb, while measures of Pb in urine and hair are less commonly used and are of low utility (see Hu *et al.* 2007 for review).

While whole-blood Pb is the most readily available biomarker for Pb exposure (and is the basis for this evaluation of Pb levels <10 µg/dL), plasma Pb is the portion of blood Pb that is available to cross cell membranes and enter specific tissues of the body (Cavalleri *et al.* 1978). Plasma Pb represents <5% of the whole-blood Pb concentration, but the proportion of whole-blood Pb in plasma Pb can vary widely and can be influenced by bone Pb levels (e.g., Hernandez-Avila *et al.* 1998, and reviewed in Hu *et al.* 1998). Measuring plasma Pb is technically difficult, requires specialized equipment not widely available, and is not typically measured in research or clinical settings (CDC 2010). Variation in whole blood or plasma collection methods and Pb quantification techniques may limit comparability across studies, particularly when a method with a relatively high level of detection is used in a population with lower Pb exposures.

The National Health and Nutrition Examination Surveys (NHANES) include whole-blood Pb measurements on a cross section of the U.S. population. Specific outcomes in subgroups of the study are routinely

published and are included in the chapters of this document covering specific health effects. General trends in blood Pb levels from NHANES data are presented in Figures 7.1, 7.2, and 7.3 (from Mahaffey *et al.* (1982), Brody, *et al.* (1994), and the CDC (2005a, 2011b) including the updated tables for CDC (2009b)).

Blood Pb levels have decreased over the last 30 years for all age groups (see **Figure 3.1**). The declining blood Pb levels follow declines in Pb exposure related to bans on leaded gasoline, paint, and use of solder in food cans and plumbing in the United States (see **Section 3.3 Sources of Pb**). Prior to the 1970's blood Pb levels were not routinely measured for research purposes, but tooth Pb measurements estimate that peak exposure occurred around 1960 and this is supported by Pb levels in lake sediments (Robbins *et al.* 2010).

Unfortunately, the burden of Pb exposure is not uniformly low in all racial and ethnic subgroups (see **Figure 3.2**). Non-Hispanic blacks have higher blood Pb levels than do non-Hispanic whites across all ages, and being non-Hispanic black is a major risk factor for higher Pb levels in children (Jones *et al.* 2009). When comparing Pb levels for non-Hispanic blacks to those for non-Hispanic whites, almost every age and gender group among blacks had Pb levels statistically significantly higher in both 1991-1994 and 1999-2002 (CDC 2005a). In a study of 249 children in Rochester, NY followed from age 6 to 24 months, black children had higher blood Pb levels even after accounting for exposure level and other modifying factors (Lanphear *et al.* 2002). Males also consistently have higher blood Pb levels than do females (see **Figure 3.3**), and this trend was observed in NHANES across most age groups and all racial/ethnic groups (CDC 2005a).

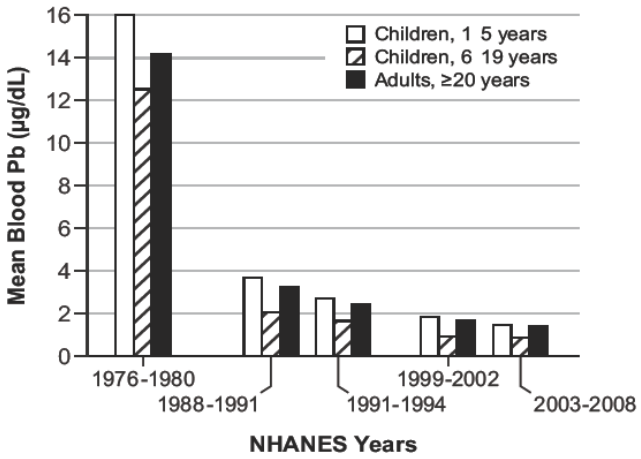
Given an accumulating body burden of Pb and higher past levels of Pb exposure, blood Pb levels are expected to go up with age; however, young children (ages 1-5 years) consistently have higher blood Pb levels than do older children, likely due to hand-to-mouth behavior in this age group (see **Figure 3.2**). Several studies show a peak in children's blood Pb levels around 24 months of age (CDC 2007b). Children are the focus of blood Pb screening and exposure reduction programs because of these higher levels and the established developmental impairments associated with Pb exposure (e.g., CDC's Childhood Lead Poisoning Prevention Program see *http://www.cdc.gov/nceh/lead/about/program.htm*) (CDC 2005b, Clark *et al.* 2011). Blood Pb levels in young children (1-5 years of age) have decreased 10-fold over the last 30 years (geometric means: for 1976-1980, 15.1 µg/dL; for 2007-2008, 1.51 µg/dL (CDC 2007b, 2011b)).

In 2008, only 0.8% of children had confirmed blood Pb levels >10 µg/dL, down from 7.6% in 1997 (*http://www.cdc.gov/nceh/lead/data/national.htm*). However, blood Pb levels have remained consistently higher in non-Hispanic black children, which may be linked to a variety of factors contributing to higher Pb exposure, such as lower socioeconomic status, living in older, urban housing, or having lower calcium intake (see **Figure 3.2**; discussed further in **Section 3.3 Sources of Pb** and **Section 3.4 Modifiers of Pb Exposure**) (Haley and Talbot 2004). Pb exposure in this critical developmental period can have immediate impacts on children's health and contribute to a lifetime of exposure from Pb.

An individual's blood Pb level reflects an equilibrium between current exogenous environmental Pb exposure and the internal (endogenous) body burden of Pb (Factor-Litvak *et al.* 1999, Brown *et al.* 2000, Chuang *et al.* 2001). The body quickly eliminates metals from circulating blood, while bone is a repository for Pb and more accurately reflects the cumulative dose of Pb integrated over years or even decades (reviewed in Hu *et al.* 1998, Barbosa *et al.* 2005, Hu *et al.* 2007). The half-life of Pb in blood is approximately 1 month, while the half-life in bone ranges from 10 to 30 years depending on the bone turnover rate, which varies by type of bone and life stage (Rabinowitz 1991). An estimated 45-70% of blood Pb comes from Pb released from endogenous tissue Pb stores, primarily in bone (Gulson *et al.* 1995).Toxicokinetic models often include other tissues within the model for blood because Pb levels rapidly equilibrate between tissues and blood (e.g., Rabinowitz 1991); however, data on turnover in other organs is limited.

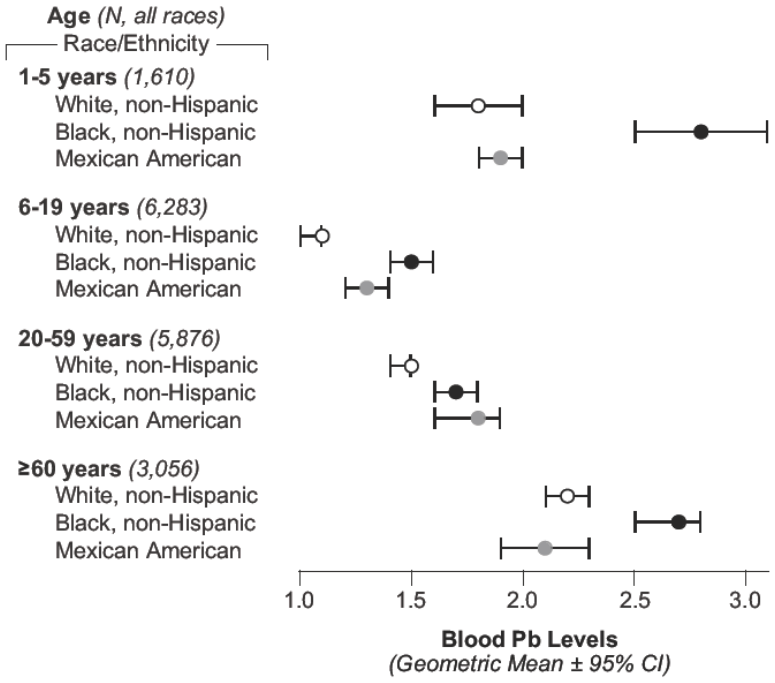
The distribution of Pb in tissues changes with life stage. The distribution is also heterogeneous within bone. Bone and teeth store 90-95% of the total body burden of Pb in adults and from 70% to 95% of the total body burden in children (reviewed in Barbosa *et al.* 2005, Hu *et al.* 2007). Bone Pb was the source of between 40% and 70% of blood Pb in individuals undergoing hip or knee replacement surgery (Smith *et al.* 1996). Pregnancy, lactation, menopause, and osteoporosis are periods of bone demineralization, which may release Pb from bone stores and contribute to increased Pb exposure to other tissues, or to

Figure 3.1: U.S. NHANES Blood Pb Levels for Children and Adults From 1976-2008



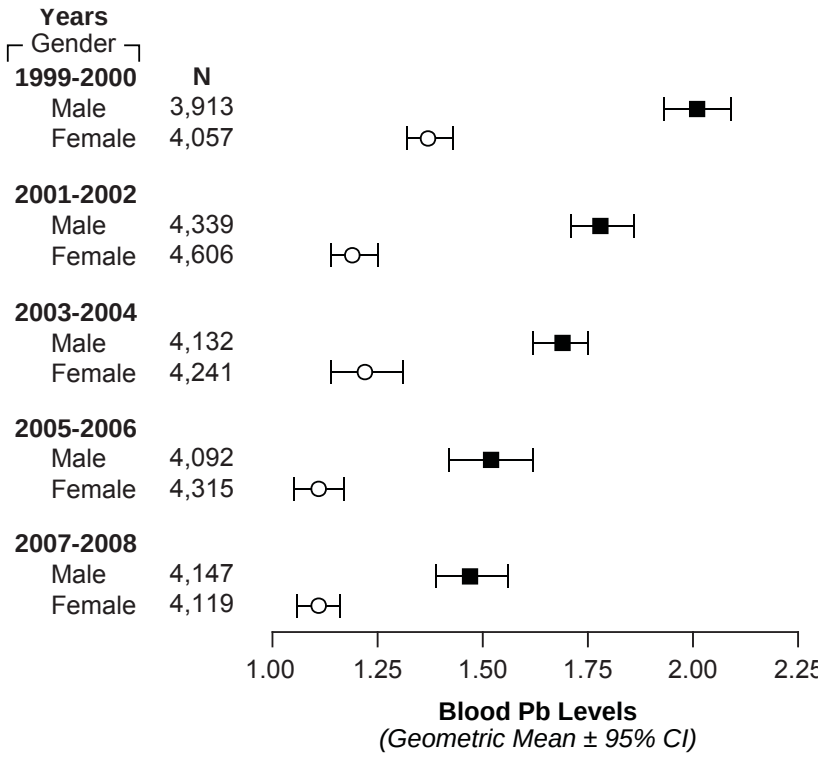
Years and ages are grouped based on available published data:
- 1976-1980 (Mahaffey *et al.* 1982)
- 1988-1991 (Brody *et al.* 1994)
- 1991-1994, 1999-2002 (CDC 2005a)
- 2003-2008 (CDC (2005a, 2011b))

Figure 3.2: U.S. NHANES 1999-2002 Blood Pb Levels Across Ages and Racial/Ethnic Groups



Mean blood Pb level and 95% CIs for different ages of non-Hispanic whites (open circle), non-Hispanic blacks (closed circle), and Mexican Americans (shaded circle) (CDC 2005a).

Figure 3.3: U.S. NHANES 1999-2008 Blood Pb Levels for All Ages of Males and Females



Mean blood Pb level and 95% CIs for men (closed squares) and women (open circles) (CDC 2011b).

Pb exposure for a developing fetus from Pb released from maternal bone. This hypothesis has been supported by several authors (e.g., Manton *et al.* 2003, Hu *et al.* 2007). In addition, there are data to support higher blood Pb levels in some groups where demineralization is expected; for example, increased blood Pb levels have been demonstrated in postmenopausal women in several studies (e.g., Silbergeld *et al.* 1988, Symanski and Hertz-Picciotto 1995, Webber *et al.* 1995, Korrick *et al.* 2002). In young children, continuous growth results in constant bone remodeling, and bone Pb is likely to be exchanged with blood Pb much more frequently than in adults (reviewed in Barbosa *et al.* 2005, Hu *et al.* 2007). Additional factors that can increase risks to women and children are discussed further in the **Section 3.4 Modifiers of Pb Exposure**.

Bone Pb is typically measured by K-x-ray fluorescence (also called KXRF); however, few research institutions possess this technology and staff trained to use it. The most commonly used KXRF devices have a high detection limit (~10 µg/g bone mineral) and a wide error of measurement, so studies that use this method may underestimate the effect on health. Newer configurations of KXRF with a lower detection limit and less measurement error may improve these estimates, particularly in populations with lower exposure to Pb (Behinaein *et al.* 2011). A more portable x-ray fluorescence device for in vivo (within the body) bone Pb measures was developed using lower energy L-band x-rays which measure Pb concentration in the outermost layer of bone (Nie *et al.* 2011). Both of these methods are impacted by the thickness of skin over the measurement site which may be a concern in health effects related to obesity. Comparison of bone Pb levels between research groups is challenging without a common standard for calibration of instruments. Another modeling approach estimates bone Pb levels from blood Pb measures and covariates typically collected in epidemiological studies (Park *et al.* 2009). This approach could be used to estimate bone Pb in existing studies that do not have the ability to measure bone Pb directly. While blood Pb is by far the most common measure of exposure, it may not be as appropriate as bone Pb, particularly for studies of chronic health conditions (reviewed in Barbosa *et al.* 2005, Hu *et al.*

2007). Physiologically based pharmacokinetic (PBPK) models have been created to combine current blood and bone Pb measures to estimate the Pb levels at the time of the exposure, allowing a more complete model of the individual's lifetime Pb exposure (Leggett 1993, Coon *et al.* 2006).

Pb has also been measured in hair, urine, and other materials that are easier to obtain; but in general Pb levels fluctuate more rapidly in these materials than in bone. Hair collection is minimally invasive, and hair is easier to ship and store; however, there are no reliable standardized protocols for hair collection, and hair is subject to contamination from environmental sources of Pb (reviewed in Seidel *et al.* 2001, Harkins and Susten 2003, Barbosa *et al.* 2005). In 2001 an ATSDR expert panel concluded that there were too many unresolved scientific issues for hair to be a useful source for evaluating exposures to trace metals, including Pb (ATSDR 2001). Collection of urine is noninvasive, and urine has also been used to measure Pb; however, urine Pb levels vary rapidly and independently of blood Pb and require correction for creatinine levels and glomerular filtration rates to estimate plasma Pb levels at a specific collection time (reviewed in Barbosa *et al.* 2005, Hu *et al.* 2007). Fecal Pb levels reflect both excreted biliary Pb and unabsorbed ingested Pb but must be completely collected over several days to accurately reflect Pb exposures (reviewed in Barbosa *et al.* 2005).

In studies designed to examine reproductive effects, Pb levels in other tissue and fluids have been measured, including semen (e.g., Naha and Manna 2007), ovarian follicles (e.g., Silberstein *et al.* 2006, Al-Saleh *et al.* 2008), and placenta (e.g., Odland *et al.* 2004, Llanos and Ronco 2009, Gundacker *et al.* 2010). Most studies report a single measure of exposure and do not directly compare the relationship between a health effect and different measures of Pb exposure (i.e., tissue Pb compared to blood Pb). Therefore, the usefulness of semen Pb, follicular Pb, or placental Pb as a measure of exposure rather than blood Pb is difficult to ascertain. At this time, blood Pb is a more widely available and is a well-established measure of exposure that is associated with multiple adverse health effects.

Unlike these fluctuating measures, teeth accumulate Pb like other bone, lose Pb at a slower rate than other bone, and for childhood exposure studies, primary teeth (baby teeth) are readily available when lost after 6 years of age (e.g., Manea-Krichten *et al.* 1991). In addition, the layers of the tooth provide a timeline of Pb exposure, including in utero (enamel) and early-childhood (primary tooth dentin) exposures, which may be separately measurable (by laser ablation/inductively coupled plasma/mass spectrometry) without removing the tooth (Uryu *et al.* 2003).

Some studies used indirect measures to estimate Pb exposure, although this is less common because whole-blood Pb measurement has become more widespread. Pb inhibits cytoplasmic enzyme δ-aminolevulinic acid dehydratase (*ALAD*), which is responsible for heme biosynthesis. Heme is a component of several iron-containing proteins including hemoglobin, the protein that transports oxygen in blood. *ALAD* can be measured in urine, blood, and plasma and is inversely related to Pb levels (reviewed in Barbosa *et al.* 2005). While not widely used, *ALAD* levels in blood may be a better marker of long-term exposure than blood Pb measures, but urine *ALAD* is not sensitive and so is not a good indicator at low Pb exposure levels (Alessio *et al.* 1981, Telisman *et al.* 1982). Pb can also impair heme formation by inhibiting ferrochelatase such that zinc is used in place of iron, increasing levels of zinc protoporphyrin (ZPP) (reviewed in Barbosa *et al.* 2005). ZPP levels in blood have been used as an indicator of Pb poisoning, but ZPP testing is not sensitive when blood Pb levels are <25 µg/dL (Wildt *et al.* 1987, Parsons *et al.* 1991, Labbe *et al.* 1999).

3.3 Sources of Pb

The primary routes of exposure in the general population are oral exposure to Pb from ingesting contaminated water and food or inhaling air and soil containing Pb. For an extensive discussion of environmental sources of Pb, see the EPA's 2006 AQCD (U.S. EPA 2006). Hand-to-mouth behavior in young children increases their risk of exposure to Pb in dust, toys, and paint. Occupational exposures in Pb industries are often associated with elevated Pb levels in workers and can also contribute to Pb exposures in coworkers who do not work with Pb, or in family members exposed to dust brought into the home from the person who works with Pb (Hipkins *et al.* 2004).

Tap water once contributed to as much as 10-20% of total Pb exposure in the United States before amendments to the Clean Water Act (U.S. EPA 2006), and some older pipes, taps, and pre-1986 pipe

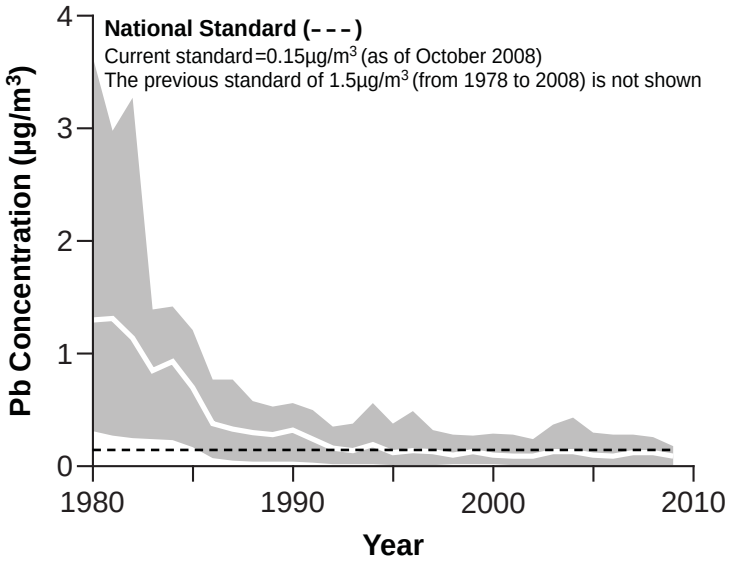
solder still contain Pb. Source drinking water rarely contains Pb, and the Pb enters tap water through corrosion of Pb from pipes and plumbing fixtures. Corrosion creates exposure from Pb deposits even after previous sources of Pb have been removed from water lines, as well as actual Pb pipes or Pb solder. This corrosion can significantly increase the Pb content in drinking water after changes in water disinfection processes, particularly with use of chloramine (Miranda *et al.* 2007, Jean Brown *et al.* 2011). In a highly publicized incident, the District of Columbia's water supply exceeded the 15 µg/L action level for Pb several times between 2000 and 2004 because of corrosion of Pb scales in service pipes after a switch to chloramine to reduce disinfection byproducts (U.S. EPA 2007). Monitoring in homes with Pb service lines in the district found a small increase in the incidence of blood Pb levels >5 µg/dL, but not over the 10 µg/dL CDC level of concern for children; however, further analysis showed that children in homes with Pb service lines were at risk for blood Pb levels >10 µg/dL even during periods when Pb levels in water were below the action level (CDC 2004, Jean Brown *et al.* 2011). In addition, the incidence of blood Pb levels >10 µg/dL was increased in infants less than 1.3 years of age during the DC drinking water event (Edwards *et al.* 2009). Infants may be at an increased risk from contaminated water if they drink infant formula made with tap water, because they typically consume 6 oz/kg of formula daily, so infants may have higher exposure relative to body weight than do others in the same household (Bearer 1995).

Dietary Pb sources in the United States have been reduced through several changes in practice, such as removing Pb solder from cans and banning Pb-arsenate pesticides (Bolger *et al.* 1996), and current Pb levels in the U.S. food supply are low (CDC 2010). Contaminated food, particularly if imported from other countries, can be a source of dietary Pb exposure. A study of pregnant women in Monterey, California, identified prepared grasshoppers sent from Oaxaca, Mexico, as a source of Pb poisoning (Handley *et al.* 2007), and tamarind candies imported from Mexico were linked to several cases of Pb poisoning in children (CDC 2002). Spices, herbs, nutritional supplements, and traditional medicines have been shown to contain or be contaminated with Pb as well (Ko 1998, CDC 1999, 2002, Buettner *et al.* 2009, Lin *et al.* 2010). Pottery with a Pb glaze can contaminate food if used for cooking or storage (CDC 2010). While high, acute exposures have been reported from Pb from pottery leaching into food (Matte *et al.* 1994), long-term use may cause a low, chronic exposure and raise the body burden of Pb (Hernandez Avila *et al.* 1991). Use of Pb-glazed ceramics was a major source of cumulative Pb exposure in a study of women in Mexico (Brown *et al.* 2000). Pb crystal glassware can release Pb into alcoholic beverages at levels above the EPA's maximum allowable level for drinking water (Graziano and Blum 1991). In addition, approximately 25% of home-distilled alcohol (moonshine) samples tested by the U.S. Bureau of Alcohol Tobacco and Firearms between 1995 and 2001 had Pb concentrations >400 µg/dL from the use of inappropriate materials in the distillation process (e.g., car radiators or welded metal parts). These concentrations are high enough to produce blood Pb levels >25 µg/dL if one liter was consumed (Morgan *et al.* 2004). Moonshine consumption has been associated with blood Pb levels >15 µg/dL and Pb-related deaths (Pegues *et al.* 1993, Kaufmann *et al.* 2003).

Inhaled Pb is another source of Pb exposure (U.S. EPA 2006). During the renovation of buildings built before 1978, dust from Pb paint can be inhaled, and residual contamination after a renovation with inadequate cleanup may continue to expose building occupants to Pb. The U.S. Department of Housing and Urban Development estimated that 40% of U.S. housing contains Pb paint, which presents a potential Pb hazard when it is disturbed or deteriorates (HUD 2001). Leaded gasoline is another inhaled source of Pb in parts of Asia, Eastern Europe, the Middle East, and South America. In the United States, leaded gasoline was banned in 1996 after being phased out for more than 20 years, and average ambient air Pb levels fell 93% between 1980 and 2009 (**Figure 3.4**) (U.S. EPA 2006). While Pb paint and leaded gasoline are no longer major sources of Pb in the United States, Pb from these sources remains in soil and dust, as well as inside people's bodies in bone and other organs as part of the body burden of Pb from earlier exposures to Pb paint and leaded gasoline (U.S. EPA 2006, Zota *et al.* 2011).

Smoking or exposure to passive smoke may lead to increased exposure to Pb in environmental tobacco smoke (ETS). Tobacco itself contains Pb, in part at least, from ambient air sources: the levels of Pb in mainstream smoke from Canadian-grown tobacco

Figure 3.4: U.S. Pb Air Concentration From 1980-2009



U.S. Pb air concentration (µg/m^3) from 1980-2009 based on annual maximum 3-month average. National trend based on 20 sites. U.S. Environmental Protection Agency *(http://www.epa.gov/air/airtrends/lead.html, accessed 1 August, 2011).*

cigarettes decreased by 62% from 1968 to 1988 as ambient air Pb levels declined (Rickert and Kaiserman 1994). Serum cotinine (a metabolite of nicotine that can be used as a biomarker of tobacco exposure) and postnatal exposure to ETS were significantly associated with blood Pb levels of children in NHANES III; these levels did not decrease with age, indicating inhalation was more likely than hand-to-mouth behavior in younger children (Lanphear *et al.* 2000, Mannino *et al.* 2003). In studies of outcomes causally linked to ETS exposure, such as neurodevelopment or cardiovascular disease, ETS may confound the observed associations of Pb and the health effect (CDC 2005a).

Contaminated soil also contributes to Pb exposure in humans if inhaled as dust or eaten. Ingested Pb from soil is 26% bioavailable when consumed on an empty stomach and 2.5% bioavailable after a meal (Maddaloni *et al.* 1998). Clay tablets sold in Mexico, Central America, and parts of Africa are eaten for religious reasons, health promotion, or simply taste and texture (CDC 2010). Children and people (particularly pregnant women) with pica, a disorder causing an urge to eat nonfood items, such as dirt or chalk, can also ingest Pb (Klitzman *et al.* 2002).

Children are most commonly exposed to Pb in paint, household dust, and soil–particularly if they reside in pre-1978, deteriorated housing–and can increase their risk of exposure by natural mouthing tendencies (Lanphear *et al.* 1998, U.S. EPA 2006). There are few direct data on Pb absorption from toys or other consumer products, but it is clear that Pb is absorbed from toys in some cases. Pb concentration in toys is mainly associated with use of Pb in paints, coloring agents, and plastic stabilizers in polyvinyl chloride (PVC) plastics (Godoi *et al.* 2009, Greenway and Gerstenberger 2010). A 4-year-old boy had an extremely high Pb level (123 µg/dL blood Pb) after swallowing a vending machine necklace pendant that contained 39% Pb (VanArsdale *et al.* 2004), and similar products could cause lower Pb exposure levels if chewed but not swallowed. Publications have not been identified that provide quantitative measures of the differences in Pb absorption between Pb paint and Pb embedded in plastics as a coloring agent or stabilizer. However, Sanchez-Nazario *et al.* (2003) demonstrated that toy chewing, along with Pb levels in window sills and soil eating habits, were significant predictors of blood Pb levels in children. Toy chewing may be a route of dust ingestion as well as absorption of Pb from the toy. Children may be exposed to Pb in other consumer products, including plastic window blinds, Pb core candle wicks, or backpacks (Sanborn *et al.* 2002).

Renovating, repairing, or painting a pre-1978 building can release particles of Pb-based paint and is associated with increases in blood Pb levels in children and adults who live in the home (CDC 2009a, 2011a). Thorough cleaning after completion of remodeling is effective in removing most of the Pb dust from a renovated residence (Yiin *et al.* 2004). Proper maintenance of housing by people trained in lead-safe practices, focusing on residential complexes with previous cases of elevated blood Pb levels, can prevent future Pb exposures (CDC 2005b). Construction and painting also contribute to occupational Pb exposures (CDC 2011a). Contractors engaged in renovation or remodeling must be certified through the EPA Lead-Safe Certification Program and use safe work practices to reduce Pb exposures to their clients, employees, and themselves. Additional certification at the state or Federal level is required for abatement to permanently eliminate Pb-based paint hazards from a home (*http://www.epa.gov/lead/pubs/traincert.htm*).

Some hobbies or recreational activities are potential sources of Pb exposure (e.g., Sanborn *et al.* 2002). Hobbies include furniture refinishing, jewelry making, creating stained glass, print-making, enameling copper, casting bronze or lead figurines, leaded glass blowing, working with Pb solder on electronics, and using Pb-containing paints or pottery glazes (CDC 2010). Fishing and hunting can contribute to Pb exposure when making fishing weights, casting ammunition, or eating animals contaminated with Pb after ingesting Pb shot or fishing weights (CDC 2010, 2011a). Air Pb levels in indoor firing ranges were significantly higher in ranges that used powder charges (660 µg/m^3) than in those that used air guns (4.6 µg/m^3) or in archery ranges (0.11 µg/m^3), and blood Pb levels were significantly higher for marksmen using powder charges during the indoor shooting season (Svensson *et al.* 1992). Pb exposures from these hobbies can be significant: a potter and her family experienced elevated Pb levels from Pb glazes used in a home studio (48 µg/dL for the potter, 54 µg/dL for her daughter, and 20 µg/dL for her husband), and a man whose hobbies included melting Pb weights to make figurines and shooting firearms at an indoor firing range had a blood Pb level of 39 µg/dL (Fischbein *et al.* 1992).

Occupational exposures to Pb occur in more than 100 industries where Pb or Pb-containing materials are used or disturbed by workers (CDC 2010). Approximately 95% of all elevated blood Pb levels reported in adults in the United States are work-related (CDC 2011a). The prevalence rate of workers with blood Pb levels >25 µg/dL decreased by more than 50% from 1994 to 2009 (from 14 to 6.3 per 100,000 adult workers), and in 2009 the Adult Blood Lead Epidemiology and Surveillance (ABLES) program lowered their definition for elevated blood Pb level from 25 to 10 µg/dL because of increased concern over health risks from lower blood Pb levels (ABLES 2009). The lowest blood Pb level required to be reported under state laws varies by state; however, of the 10 states that collected all test levels in 2004, 32% of women with blood Pb >5 µg/dL reported occupational exposures, mostly in manufacturing (CDC 2007a). Occupational sources of Pb can also expose workers' families because Pb dust travels home on clothes and in vehicles (Hipkins *et al.* 2004, CDC 2009c). Living near Pb mining, smelting, and manufacturing sites may expose the surrounding community to low Pb levels, particularly in countries without environmental regulations or monitoring programs (Benin *et al.* 1999). These groups have been the subject of many older studies of health effects associated with Pb exposure and continue to be a source of study subjects with higher exposure levels (e.g., a study of birth outcomes for women living near a Pb smelter plant with a damaged pollution-control device Berkowitz *et al.* 2006).

Because the focus of this evaluation is on blood Pb levels <10 µg/dL, studies with mean blood Pb levels >15 µg/dL were not included in this evaluation except as specified in **Section 8.0 Reproductive/Developmental Effects** (e.g., groups in studies by Kromhout *et al.* (1985) and Locket and Arbuckle (1987) had mean blood Pb levels ≥15 µg/dL and were not included in the evaluation of cardiovascular effects). Stratified analyses of only subjects with Pb levels above and below 10 µg/dL have indicated that associations with some health effects can be stronger at lower exposure levels (e.g., Pb-related intellectual deficits (Lanphear *et al.* 2005)). Excluded occupational studies were mostly older publications on workers with mean blood Pb levels >10 µg/dL or on workers without occupational monitoring programs. Even with the ABLES definition of elevated blood Pb as 10 µg/dL, Pb-exposed workers can have higher blood levels than the general population and a higher lifetime burden of Pb from long-term exposures.

3.4 Modifiers of Pb Exposure

Individual-level differences in exposure and biology affect the amount of Pb that reaches a target tissue to impact health. These differences may influence contact with environmental Pb, as well as Pb metabolism and remobilization of Pb stores. Modifiers of Pb exposure include age, life stage, gender, diet, socioeconomic status, immigrant status, and genetic variants. These factors are often correlated with one another as well.

Blood Pb levels increase with age from bone Pb stores that accumulate over time, as previously discussed in **Section 3.2 Biomarkers of Pb Exposure**. Before bans on Pb in paint, solder, and gasoline, environmental Pb levels in the United States were higher, so older adults accumulated more Pb as children than children do today. Several authors have suggested that the aging process contributes to Pb exposure as bone begins to deteriorate, particularly if coupled with osteoporosis (Silbergeld *et al.* 1988, Campbell and Auinger 2007). The data supporting this hypothesis come from cross-sectional studies and therefore the studies are only able to infer the temporal sequence. A particular challenge comes in relating increased blood Pb levels to mobilization of Pb from bone stores due to osteoporosis, because animal studies have demonstrated that Pb exposure results in lower bone density or bone strength (Hamilton *et al.* 1994, Ronis *et al.* 2001) and support a causal effect of Pb on bone density, rather than the other way around. A study of adults in New York found that age was not a risk factor for higher blood Pb levels (≥10 µg/dL) (Gelberg and Fletcher 2010); however, blood Pb levels <10 µg/dL were not reported. Recent NHANES data support an association between higher blood Pb levels and increased age in older children and adults with generally low blood Pb levels (well below 10 µg/dL; see **Figure 3.2**) (CDC 2005a). Young children are an exception to this age trend and have higher blood Pb levels than do infants and older children (CDC 2007b).

Young children show marked increases in blood Pb levels after birth, with a peak around 2 years of age (Rothenberg *et al.* 1999b). Initially, maternal sources of Pb could contribute to a child's exposure levels. Mothers' blood Pb levels at delivery are highly correlated with umbilical cord blood Pb levels, with umbilical cord blood levels slightly lower (Graziano *et al.* 1990, Rothenberg *et al.* 1999b). The CDC concluded that in utero exposure risks to children are greatest if mothers had a significant past Pb exposure (CDC 2010). Maternal blood and milk Pb levels are correlated as well, but the efficiency of Pb transfer from blood to milk varies at low levels, and Koyashiki *et al.* (2010) concluded that there are no established health risks from breast milk. Current CDC guidelines are to continue breastfeeding up to high blood Pb levels (40 µg/dL blood Pb levels in the mother) (CDC 2010). A study in mice showed that gestational and lactational Pb exposure from the mother increases Pb levels in the offspring, with declining blood Pb levels after weaning (Snyder *et al.* 2000). There is some evidence that Pb from dietary sources is more readily absorbed and retained in young children and infants than in adults (Ziegler *et al.* 1978). Young children are also exposed to environmental Pb because of normal mouthing behaviors, as discussed in **Section 3.3 Sources of Pb**. A number of authors have hypothesized that blood Pb may provide a better measure of Pb exposure in children because of highly active bone remodeling (see reviews by Barbosa *et al.* 2005, Hu *et al.* 2007). However, other than studies that examined Pb levels in shed primary teeth, few studies in children have examined the usefulness of bone Pb data as a measure of exposure in children that might be associated with health effects of Pb.

On average, adult men have higher levels of Pb in blood and bone than do adult women, and men are much more likely to be exposed to occupational sources of Pb. However, women typically go through more stages of life where demineralization of bone may be associated with mobilization of bone stores Pb into circulating Pb. Therefore, a number of authors have supported the hypothesis that women are at risk from increased blood Pb levels mobilized from bone stores during pregnancy and menopause and due to osteoporosis (e.g., Silbergeld *et al.* 1988, Manton *et al.* 2003, Hu *et al.* 2007). Blood Pb levels in pregnant women are generally low in the United States (NHANES geometric mean <5 µg/dL) and do not vary by the age of the mother (Jones *et al.* 2010). Pregnancy-associated increases in blood Pb have been demonstrated in a number of case studies (e.g., Rothenberg *et al.* 1992, Shannon 2003), but the overall pattern of blood Pb throughout pregnancy appears to be complex (Hertz-Picciotto *et al.* 2000, Schell *et al.* 2000). Blood Pb levels follow a U-shaped curve during pregnancy, decreasing during weeks 12-20 and then increasing linearly over the second

half of pregnancy (Rothenberg *et al.* 1994). Overall blood Pb levels decrease during subsequent pregnancies, so the first pregnancies pose the most risk of Pb toxicity, particularly if the mother had significant past Pb exposures (Manton *et al.* 2003, CDC 2010). A number of studies have demonstrated increased blood Pb levels in postmenopausal women (e.g., Silbergeld *et al.* 1988, Symanski and Hertz-Picciotto 1995, Webber *et al.* 1995, Korrick *et al.* 2002, Nash *et al.* 2004). Data from Symanski *et al.* (1995) also support a greater relative increase in blood Pb levels in postmenopausal women that have never been pregnant, supporting both increased mobilization of Pb associated with menopause as well as mobilization and clearing of body burdens of Pb during pregnancy. To a lesser extent, studies also support increased blood Pb levels associated with osteoporosis (e.g., Campbell and Auinger 2007), although as discussed above, studies in laboratory animals demonstrate that Pb exposure causes reduced bone density and therefore cause-and-effect is particularly difficult to establish between osteoporosis and blood Pb levels.

Nutritional deficiencies can be related to Pb levels. Deficiencies in calcium, iron, and zinc were associated with increased Pb levels at 6 months of age, and iron deficiency continued to be associated with Pb at 12 months of age (Schell *et al.* 2004). Low iron intake may contribute by increasing Pb absorption in these infants, who had a mean 12-month blood Pb level of 5.1 µg/dL (Schell *et al.* 2004). In older people, calcium deficiency can increase bone turnover and circulating Pb levels (CDC 2010). Pb absorption is higher when there is less food in the digestive tract, making dietary habits and gastric emptying rates another source of individual variation in the body burden of Pb (James *et al.* 1985, Maddaloni *et al.* 1998).

Low socioeconomic status (SES) is associated with higher blood Pb levels (e.g., Wibowo *et al.* 1986, Greene *et al.* 1992, Schnaas *et al.* 2004, Bellinger 2008). People with low SES may be exposed to a collection of risk factors, including living in older, deteriorated housing with Pb in paint, household dust, pipes, or urban air; consuming diets lower in nutrients and calories; playing with potentially contaminated inexpensive toys; working in jobs with occupational Pb exposure; and other environmental hazards (reviewed in Sexton 1997, Strike and Steptoe 2004). The best strategy for preventing new Pb exposures in housing is to remove the Pb paint and dust, but authors such as Wakefield *et al.* (2002) have noted that Pb abatement can cost over $10,000 per home, and they suggest that this cost may result in remediation of less than 0.1% of seriously dangerous homes per year. Care has to be taken during the remediation, and workers performing the job should receive special training, because as discussed earlier, general repair and renovation can be associated with increased Pb exposure and higher blood Pb levels in building occupants and workers performing the repairs (CDC 2009a, 2011a).

Many immigrants face SES-related exposure risks, but they may have additional risk factors as well. If their home country has relatively high Pb exposure levels, immigrants carry a larger body burden of Pb (CDC 2010). Exposure to leaded gasoline emissions, as estimated from time spent in Mexico City, was a major source of cumulative Pb exposure in a study of postpartum women in Mexico (Brown *et al.* 2000). In a study of pregnant women, a Pb-related increase in blood pressure was only seen in immigrants, predominantly from Latin America, even without markedly higher blood Pb levels than nonimmigrants (Rothenberg *et al.* 1999a). In some cultures, pica during pregnancy is common and accepted (CDC 2010). In a study of pregnant women in New York, pica was the most frequently reported source of Pb exposure (13 women, 39% of those with levels >20 µg/dL) (Klitzman *et al.* 2002). Immigrant status could increase exposure to Pb contaminated products, including alternative remedies, imported cosmetics or food items, or Pb-glazed pottery for cooking or food storage (CDC 2010). Women in the United States using herbal supplements had higher blood Pb levels, particularly in those using St. John's wort or Ayurvedic or traditional Chinese medicinal herbs (Buettner *et al.* 2009).

Biological variation in Pb absorption and metabolism rates can be partially explained by genetic variation. The relationship between Pb exposure and a particular health effect may be modified by the presence of a single nucleotide polymorphism (i.e., variation in a single DNA nucleotide between individuals or groups) or by other genetic variations. When studying genetic risk factors in observational studies, selection for the study is independent of genotype, which remains unknown to the subject, so sources of bias that may confound other risk factors are minimized. If specific genetic variants are found to increase or decrease the association of Pb with a

health effect, there is a stronger biological basis for that relationship, and the gene function may give an indication of the mechanism of action. Genes studied for variations in Pb metabolism include hemochromatosis (HFE) and aminolevulinate dehydratase (*ALAD*), and specific study details are presented in the appendices for each chapter.

Interactions between many of the previously discussed factors make it difficult to separate the increases in risk from each individual factor. While many measures taken to reduce Pb exposure have decreased blood Pb levels in the U.S. population, economically disadvantaged young children in older housing or pregnant immigrants using contaminated products are still at risk for significant Pb exposures.

3.5 Summary

While Pb can be measured in a variety of human tissues, whole-blood Pb is the most common measure used in both research and clinical settings. Blood Pb levels fluctuate and represent both current exposures from the environment and internal (endogenous) sources of Pb, primarily stored in bone. Bone Pb is a better measure of the cumulative body burden of Pb and therefore it is commonly hypothesized that bone Pb may show more consistent associations with long-term health effects. Pb continues to be used in industrial processes and in manufactured products in the United States and worldwide and is persistent in the environment. Humans are exposed to Pb via water, air, soil, food, and consumer products. Several Pb reduction efforts have significantly reduced exposure levels over the last 30 years, and blood Pb levels have dropped considerably in the United States. Pb exposure levels vary greatly by age, life stage, gender, and socioeconomic level; and even at low levels with blood Pb <10 µg/dL there are health risks. The other chapters of this document outline the evidence for specific health effects from blood Pb levels <10 µg/dL. A discussion of Pb exposures in potentially susceptible populations for specific health effects is included in individual chapters.

EXHIBIT 7

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Article

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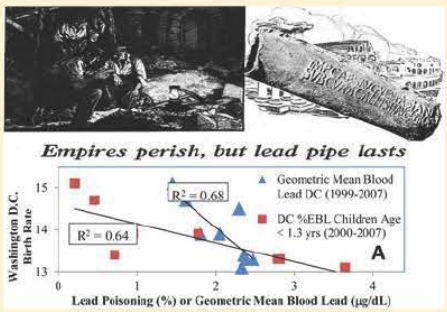
Fetal Death and Reduced Birth Rates Associated with Exposure to Lead-Contaminated Drinking Water

Marc Edwards*

Civil and Environmental Engineering Department, Virginia Polytechnic Institute and State University, 418 Durham Hall, Blacksburg, Virginia 24061, United States

Supporting Information

ABSTRACT: This ecologic study notes that fetal death rates (FDR) during the Washington DC drinking water "lead crisis" (2000–2004) peaked in 2001 when water lead levels (WLLs) were highest, and were minimized in 2004 after public health interventions were implemented to protect pregnant women. Changes in the DC FDR vs neighboring Baltimore City were correlated to DC WLL ($R^2 = 0.72$). Birth rates in DC also increased versus Baltimore City and versus the United States in 2004–2006, when consumers were protected from high WLLs. The increased births in DC neighborhoods comparing 2004 versus 2001 was correlated to the incidence of lead pipes ($R^2 = 0.60$). DC birth rates from 1999 to 2007 correlated with proxies for maternal blood lead including the geometric mean blood lead in DC children ($R^2 = 0.68$) and the incidence of lead poisoning in children under age 1.3 years ($R^2 = 0.64$). After public health protections were removed in 2006, DC FDR spiked in 2007–2009 versus 2004–2006 ($p < 0.05$), in a manner consistent with high WLL health risks to consumers arising from partial lead service line replacements, and DC FDR dropped to historically low levels in 2010–2011 after consumers were protected and the PSLR program was terminated. Re evaluation of a historic construction related miscarriage cluster in the USA Today Building (1987–1988), demonstrates that high WLLs from disturbed plumbing were a possible cause. Overall results are consistent with prior research linking increased lead exposure to higher incidence of miscarriages and fetal death, even at blood lead elevations (≈5 μg/dL) once considered relatively low.



INTRODUCTION

The Washington DC (DC) "lead in drinking water crisis" caused an increased incidence of elevated blood lead (EBL) in children at thresholds >5 μg/dL and also >10 μg/dL.[1−3] The "lead crisis" was inadvertently triggered in 2000 by a switch in drinking water disinfectant from chlorine to chloramine (Table 1) to reduce regulated disinfection byproducts, but the switch also caused an unintended release of lead from plumbing materials to drinking water.[1−6] Consumers had no warning of high water lead levels (WLLs) until late 2002, and the true extent of the hazard was not publicly revealed until a front page investigative Washington Post report in January 2004.[2,7] Unprecedented interventions by the DC Department of Health (DC DOH) were then implemented to protect the general public and especially sensitive populations of pregnant women including written and broadcast (radio, television) alerts to avoid tap water, use utility provided water lead filters or enhanced flushing of pipes.[1,4,7,8] These interventions dramat ically reduced the incidence of childhood lead poisoning (i.e., blood lead >10 μg/dL for children under age 6) in DC from 2004 onward.[2]

Exposure to lead has been associated with spontaneous abortion, stillbirth and high rates of infant mortality.[9,10] Lead abortion pills with 32 μg lead each (256 μg Pb per day for the recommended dose of 8 pills) were used in the early 1900s, and use of new lead pipe in potable water systems for cities without corrosion control increased fetal mortality 300–400%.[9,10] On this basis a significant elevation in miscarriage and fetal death rates would be predicted in Washington, DC from late 2000 through 2003. For instance, analysis of thousands of samples collected by the District of Columbia Water and Sewer Authority (DC WASA) in 2003 from homes with lead pipe, revealed median daily consumer exposure of 70 μg Pb/day assuming 2 L tap water exposure per day from a 50:50 mixture of first draw:flushed water. The same type of analysis indicates that greater than 15% of these consumers had daily exposure exceeding that from 1900s lead abortion pills (256 μg Pb/day).[2,9,10] The presumed historical success of the lead abortion pills via acute lead exposure, highlights concerns about adverse pregnancy outcomes from short term exposure of pregnant women in Washington, DC to elevated WLLs.

More recent research demonstrated that every 5 μg/dL increase in maternal blood lead resulted in a 180% increased

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Table 1. Demarcation of Washington DC Lead in Water Risks into Calendar Years for Consideration of Impacts on Fetal Death, Birth Rates and General Fertility

calendar year time period	consumer risk to elevated lead in water
1997 1999	low. low water lead when chlorine was disinfectant.
2000	uncertain. chloramine only dosed part of the year and no lead in water samples were taken during that time.
2001 2002	highest. very high lead in water and no public information of health risks until 10/2002.
2003	high. high lead in water and ineffective public education from 10/2002 to late 2003.
2004 2006	low. high lead in water, but intense public education, congressional intervention, provision of lead filters and enhanced flushing instructions protected population.
2007 2009	low general lead in water risks due to corrosion control, but high PSLR activity and removal of public health protections created very high risk in PSLR[a] homes.
2010 2011	very low. low water lead due to corrosion control, low risks in PSLR homes due to CDC health advisory issued 1/2010 and provision of lead filters.

[a]PSLR= partial service line replacement.

risk of miscarriage (defined herein as death of an embryo from pregnancy up to 20 weeks gestation).[11,12] While statistically robust records of maternal blood lead in DC are not available for analysis, it is likely that the increased incidence of childhood blood lead over thresholds of 5 and 10 μg/L (lead poisoning)[1−3] during the lead crisis is a reasonable proxy for trends in maternal blood lead, for which each 10 μg/dL increase would raise miscarriage rates by about 360%.[11,12]

While problems with elevated WLLs throughout DC were largely controlled after 2006 by dosing of an orthophosphate lead corrosion inhibitor (Table 1), more than 13 000 homes where lead pipes were disturbed had unusually high risk of elevated WLLs from 2004 to 2011.[3,7,8,13−15] Specifically, after the water utility cut lead service pipes to implement partial service line replacements (PSLR) under mandates of the U.S. Environmental Protection Agency (EPA) Lead and Copper Rule or through their own voluntary program from mid 2006 to 2009, consumer collected water samples often contained over 100 μg/L and as much as 190 000 μg/L lead.[8,13,14] The WLL remains elevated in the PSLR homes for a few months or years after cutting the pipe.[16] Although the Centers for Disease Control (CDC) identified increased risk of childhood lead poisoning risk incidence in DC PSLR homes in late 2007, the public was unaware of any problem until a Washington Post article in 2008, which revealed the serious spikes in WLLs and the utility began to scale back the PSLR program.[7,8,14] But consumers were not adequately protected from high WLLs until the CDC issued a public health advisory regarding an increased incidence of childhood lead poisoning in PSLR homes in January 2010, the utility provided consumers water lead filters, and the health risks were reinforced by congressional hearings and extensive media coverage (Table 1).[14,15,17] CDC eventually reported 330% increased incidence of childhood lead poisoning in PSLR homes versus DC homes without lead pipe.[3]

This research examines whether expectations of adverse pregnancy outcomes are evident in fetal death and birth rate data for Washington, DC from 2001 to 2003 when WLLs were elevated throughout the city and consumers were unprotected, and if there are also links between fetal death rates and PSLR activities from 2007 to 2009 before public health interventions protected the public from high WLLs (Table 1). To enhance the analysis, a general approach used in prior studies of infant mortality due to arsenic exposure in Chile drinking water was followed,[18] by comparing Washington, DC to neighboring Baltimore City, MD which had relatively low WLLs from 1997 to 2011. Baltimore City has a number of similarities to Washington, DC.(Table 2) and both cities are part of the same

Table 2. Representative Demographic Data for Washington DC, Baltimore City and the United States

parameter	Washington, DC	Baltimore City	United States
population	601 723	620 961	308 700 000
average family size	3.15	3.14	3.14
median household income ($)	61 835	40 00	52 762
% population in poverty	18.2	22.4	14.3
% population African American	50.7	63.7	12.6
% population women age 15 44	27.0	23.4	20.2
total housing units	296 719	296 685	131 034 946
%Pop <9th grade education	5.0	6.6	6.1

combined statistical area (CSA) census department designation due to social and economic ties, as well as geographical proximity.[19,20] The comparison to Baltimore City can eliminate many localized confounding factors that could impact comparisons between Washington, DC and the United States. A final phase of research applies an evolving understanding of consumer lead exposure that arises from disturbed lead plumbing, to a historic 1987−1988 Washington, DC area "USA Today Building" miscarriage cluster, where very high WLLs and proximity to renovation disturbances were initially implicated as a causal factor.[21−26]

MATERIALS AND METHODS

WLL and PLSR Replacement Data. DC WLL samples collected for EPA compliance monitoring (1997−2011) were organized into calendar year time periods,[2,6] for which corresponding incidence of fetal death, live birth and other data were also compiled (Table 3). The 90th percentile (90th %) water DC WLL data from 1997 to 2000 were derived from a U.S. EPA report,[6] data from 2001 to 2007 were derived from Edwards et al.,[2] and data for 2008−2011 were obtained from DC WASA consumer confidence reports.[27] Since chloramine was only dosed in part of 2000, and no WLL data were collected for that time period (and the data were subject to revision and controversy),[6] year 2000 data was excluded from any correlations between WLLs and adverse pregnancy outcomes. DC WASA provided data on PSLRs from 2003 to 2011 (Table 3) and incidence of lead pipes by neighborhood or ward.[28] Baltimore City WLL data were obtained from consumer confidence reports (2001 onward) and from the U.S. EPA before 2001 (1997−2001).[29,30]

Blood Lead Trends for Washington, DC, Baltimore City, and the United States. Washington, DC blood leads were derived from prior published independent data due to acknowledged problems with the CDC data set and DC DOH reporting.[2,7,31] Baltimore City and U.S. data on incidence of childhood lead poisoning were compiled from Baltimore City Health Department records or CDC's lead surveillance data.[32−34]

Fetal Deaths and Live Births. Data for miscarriages <20 weeks gestation are not systematically compiled and reported in

Table 3. Lead in Water, Incidence of Elevated Blood Lead (EBL), Fetal Death Rate (FDR), Birth Rate, General Fertility Rate (GFR),@ and Partial Service Line Replacements (PSLR) in Washington D.C (DC), Baltimore City (BC) and the United States (U.S.)

	Washington, DC							Baltimore City, MD					United States			
year	DC 90th% Pb[a]	% EBL DC	% EBL DC Age <1.3 yr	PSLR	FDR DC	birth rate DC	GFR DC	BC 90th% Pb[b]	% EBL BC[&]	FDR BC	birth rate BC	GFR BC	% EBL U.S.[&]	FDR U.S.	birth rate U.S.	GFR U.S.
1997	7			na	9.7	15	61.6	13		17.1	14.1	60.0	7.6	6.8	14.2	63.6
1998	7			na	9.5	14.7	60.7	8		16.9	14.9	63.0	6.5	6.7	14.3	64.3
1999	12.5	5.5		na	7.9	14.5	59.9	10	16.7	16.9	15.4	66.0	5.0	6.7	14.2	64.4
2000	34	3.8	0.71	na	10.8	13.4	53.3	12	12.1	14	14.8	63.1	4.0	6.6	14.4	65.9
2001	79	3.2	2.78	na	12.9	13.3	52.9	11	9.5	15.2	14.1	60.7	3.0	6.5	14.1	65.1
2002	45	4.2	3.65	na	10.4	13.1	52.8	8	9.4	16.3	14.2	61.5	2.6	6.4	14	65.0
2003	51.5	3.9	2.82	373	8.9	13.3	55.1	10	6.4	13	14.4	63.0	2.3	6.3	14.1	66.1
2004	59	2.7	1.78	1745	7.1	13.9	58.3	11	6.2	13.1	14.4	64.6	1.8	6.3	14	66.4
2005	15	2.7	0.95	3210	8.2	13.9	58.4		4.8	13.3	14.4	65.1	1.5	6.2	14	66.7
2006	11	1.7	0.46	3312	7.5	14.7	58.4		4.3	11.4	15.5	69.3	1.2	6.1	14.3	68.6
2007	10.5	0.9	0.21	3430	9.9	15.1	60	7	3.4	10.9	15.5	68.8	0.9		14.3	69.3
2008	7			2442	10.1	15.4	61.4			10.3	15.6	69.5	0.7		14	68.1
2009	8			411	8.2	15.1	59.7	8		10.6	14.9	63.7	0.6		13.5	66.2
2010	5			229	7.4	15.2	56.4			10.9	14.4	61.2	0.6		13	64.1
2011	5			123	6.5	15	55.9	5[b]		10.9	14.3	61.6	0.6		12.7	63.2

[a]90th% EPA Lead and Copper Rule data adjusted to calendar year from prior work[2,6] except for 2000, a year in which chloramine was first dosed and also includes a sampling round where high lead samples were illegally invalidated. The U.S. EPA issued a revised calculation for July 2000 June 2001 of 34 ppb.[6] [b]Baltimore has been on reduced monitoring since 2004 and only samples for lead in water every 3 years. Data in Table for Baltimore City in year 2011, is that reported in the 2012 Consumer Confidence report, to indicate trends from 2009 to 2011. [c]Fetal death rates (FDR) per thousand births are calculated for DC and Baltimore City using a standard formula [FDR = (no. fetal deaths)/(live births + fetal deaths)] × 1000; birth rates are live births per thousand population, general fertility rate (GFR) is number of live births per thousand women aged 15−44.

the U.S., but total fetal deaths (over 20 weeks gestation) and live births for Washington, DC are compiled and reported annually by the DC DOH to Vitalstats Online.[35] Total fetal deaths (over 20 weeks) in Washington, DC reported and compiled by DC DOH, were taken from Vitalstats (1997−2005) and DC DOH reports (2003−2011).[35−37] Data on Washington, DC birth rates, general fertility rates, and births by ward (neighborhood) were obtained from DC DOH reports or Vitalstats.[35−38] Fetal death rates, birth rates and general fertility rates for Baltimore City 1997−2011 were obtained from annual Maryland Vital Statistics reports,[39] and similar data for the United States were obtained from National Vital Statistics reports when available.[35,40,41]

Effects of Renovation Activity on Lead Release from Soldered Plumbing. Trends in lead release to potable water occurring as a result of vibrations during renovations were investigated experimentally. Six 0.6 m long copper pipes (1.9 cm diameter) with a single central joint and a 6″ bead of 50:50 Pb:Sn solder were created and exposed to simulated source water for the USA Today building (synthesized Potomac River water).[2] The pipes were first conditioned in a continuous recirculation mode for 3 months using a 150 L reservoir to allow development of a lead corrosion product (rust) layer, that might be mobilized to water during physical disturbances.[42] Water in the reservoir was completely changed each month throughout the study. Thereafter, baseline lead release to the recirculating reservoir was quantified for each pipe after 1 month exposure, using a representative premise plumbing flow regime of 15 s flow every 8 h at 0.66 m/sec. The pipes were then gently placed directly on a concrete pad at distances of either 3 or 15.2 m from a conventional jackhammer, weighed down with 20 kg masses to hold the pipes firmly in place, and the jackhammer was operated 30 s to generate representative vibrations that arise during renovation. The pipes were then placed back into the recirculation reservoir which was sampled (as before) at 1 and 4 months after the vibration disturbance (months 2 and 3 were not sampled).

Statistical Methods and Error Bars. Correlations, statistical testing, and upper and lower confidence intervals were calculated using a standard Microsoft EXCEL 2010 program with an assumption that data were normally distributed. All error bars in graphs represent 95% confidence intervals.

RESULTS

After reviewing temporal trends in DC fetal death rates from 1997 to 2011 as a function of WLL risk (Table 1), a similar analysis was conducted for birth rates. Results of a simulation experiment quantifying trends in lead release to water from pipes disturbed during construction renovation are then described, providing a basis for reconsidering the possible role of elevated WLLs in the USA Today miscarriage cluster.

Changes in Fetal Death Rates: Washington, DC, 1997−2011. The 90th percentile WLL in DC (Table 3) spiked over 40 μg/L from 2001 to 2004 after the switch to chloramine disinfectant, with a peak WLL of 79 μg/L in calendar year 2001.[2] Prior work indicated that during 2001, incidence of childhood lead poisoning (blood lead >10 μg/dL) increased from 0.5% up to 4.8% for children less than 1.3 years of age.[2] The DC fetal death rates declined from 9.7 down to 7.9 per thousand births in the years 1997−1999 before chloramine was dosed to water (Table 3), but increased 32−63% when WLL was high in 2001 (Figure 1A). Fetal death rates remained high in 2002, and did not drop below those of 1999 until public health interventions in 2004 decisively limited exposure of pregnant women to high WLLs.[2,7] Applying a dummy variable of 90th% lead of 10 ppb to reflect lower exposure due to the consumer public health protections from 2004 to 2006,

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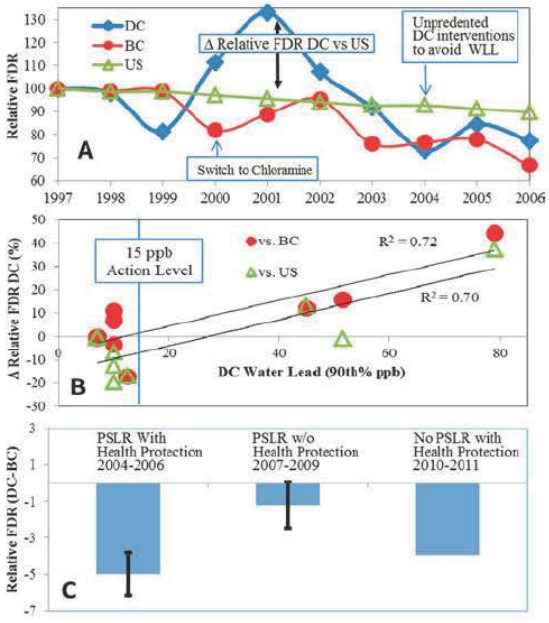

Figure 1. Relative fetal death rates (1997 = 100%) trended downward in the U.S. and in Baltimore City (BC) from 1997 to 2006, but exhibited a spike in DC around 2001 when lead in water was high (A). The change in relative fetal death rates (FDR) for DC versus BC or versus the U.S. was strongly correlated to water lead level (B; Figure excludes transition year of 2000). In years with partial lead service line replacements (PSLR) and no public health protections in 2007–2009, fetal death rates rose in DC to the point they were not statistically different from BC, before dropping back when PSLRs were discontinued and public health protections were offered residents in 2010–2011 (C).

indicates that higher WLL correlated to higher fetal death rates from 1997 to 2006 (R^2 = 0.60; data not shown excluding year 2000).

WLLs in Baltimore City (BC) declined steadily from 1997 to 2012 from 13 ppb down to 5 ppb (Table 3), along with incidence of childhood lead poisoning (16.7% in 2000 to 3.4% in 2011) and fetal death rates (17.1 down to 10.9 per thousand births). U.S. fetal death rates (6.8 to 6.1 per thousand births) and lead poisoning incidence (7.6 to 1.2%) also declined steadily from 1997 to 2006 (Table 3). After normalizing fetal death rates in DC, BC, and the U.S. by setting 1997 rates to 100% (Figure 1A), the 2000–2003 trend in DC is observed to be anomalously high. The higher rate of fetal deaths in DC versus either the U.S. or BC correlates (R^2 = 0.70–0.71) to the DC 90th% lead level (assuming 10 ppb lead as a dummy variable reflecting lower WLL exposure in 2004–2006 and excluding year 2000; Figure 1B). The correlation does not change significantly if years 2004–2006 are simply excluded from the analysis (R^2 = 0.70–0.72; data not shown). If the relative fetal death rate is calculated on an absolute rather than a percentage basis, a significant but somewhat lower correlation with DC 90th% WLL is observed (SI Figure 1; R^2 = 0.45 DC versus BC; R^2 = 0.68 DC vs U.S.). The correlation improves if years 2004–2006 are excluded from the analysis rather than using a dummy variable to reflect lower WLL exposure (R^2 = 0.62 DC versus BC; R^2 = 0.82 DC vs U.S.).

After DC experienced 3 years of relatively low fetal death rates (7.1–8.2 per thousand births) from 2004 to 2006 when the public health protections for high WLLs were in place (Table 1; Table 3), fetal death rates rose 21–42% to 9.9–10.1 per thousand births in 2007–2008 when risks of high WLLs in PSLR homes were highest and consumer public health protections were removed. DC fetal death rates declined smoothly from 2008 to 2011 as the PSLR program was phased out and public health protections were reinstituted in early 2010. During this same time period 2004–2011, fetal death rates declined or remained stable in BC. Analysis of relative fetal death rates confirm an adverse change in DC from 2007 to 2009, as DC fetal death rates rose to the point they were not statistically different from those in BC. DC fetal death rates are much lower than in BC in either 2004–2006 ($p < 0.05$) or in 2010–2011 when public health protections were in place (Figure 1C).

Changes in Birth and General Fertility Rates: Washington, DC, 1997–2006. Birth rates in DC decreased from 1997 to 1999 to 2001–2003 as WLLs rose during the lead crisis, and then increased by more than 0.6 births per thousand residents ($p < 0.05$) after public health protections were implemented from 2004 to 2006 (Table 3). Birth rates in DC continued to rise steadily from 2006 to 2009. Incidence of childhood lead poisoning and median child blood lead are possible proxies for trends in maternal blood lead (Table 3), and the DC birth rate was inversely correlated to both parameters (Figure 2A; R^2 = 0.64–0.68).

A neighborhood (ward) analysis indicated that the higher birth rates for 2004 vs 2001 in DC, were highly concentrated in the wards of the city with the highest incidence of lead pipe and WLL exposure. The presence of a lead service pipe increased

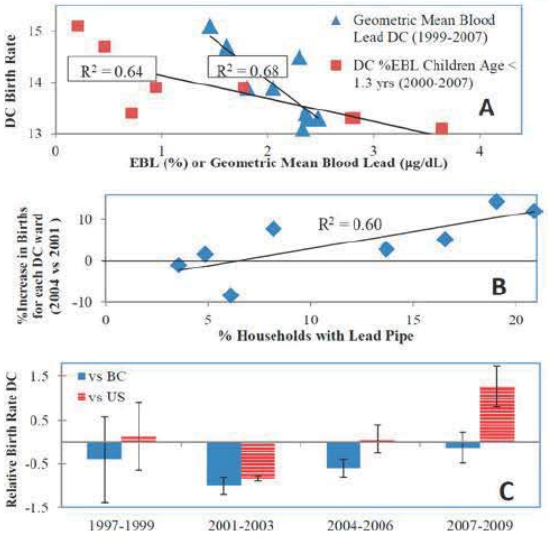

Figure 2. The birth rate in DC was inversely correlated with geometric mean blood lead and the percentage of children <1.3 years of age with blood lead over 10 µg/dL (A). Increased birth rates in each DC ward for 2004 versus 2001, was correlated to the percentage of lead pipes within each ward (B). Birth rates in Washington, DC relative to Baltimore City or the U.S., decreased during the lead crisis 2001–2003, and then increased in 2004–2006 when public health protections were implemented (C).

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the likelihood of high WLLs and incidence of childhood lead poisoning during the lead crisis.[1,3,6] Specifically, the two wards with greater than 19% incidence of lead pipe observed a greater than 12% increase in births for 2004 versus 2001, whereas the three wards with less than 6% incidence of lead pipe all had less than a 1.5% increase in births (or even declining birth rate) during the same time period (Figure 2B) . The percent increase in birth rate comparing 2004 vs 2001 for each ward was correlated to the incidence of lead pipe in that ward (Figure 2B; $R^2 = 0.60$).

Birth rates nationally were relatively constant in the range of 13.5−14.7 from 1997 to 2009 (Table 3), and the national birth rate actually declined slightly to 14.0 from 14.1 in 2004 vs 2003, respectively. Birth rates were unchanged in Baltimore City from 2004 vs 2003 (Table 3). The calculated changes in birth rate for DC versus either BC or the U.S. illustrated a consistent trend, with a relative reduction in birth rates for DC in 2001−2003 when WLLs are low, and relative increases in birth rates (after 2004) when the population was protected by either public health interventions or corrosion control (Figure 2C). Taking a larger perspective using National Vital Statistics data for other U.S. states and territories,[35] the 4.8% increase in DC birth rates reported in 2004 versus 2003 was the highest among U.S. states and territories reporting more than 2000 births. Likewise, the 11% increase in DC birth rates comparing 2006 versus 2003, was matched or exceeded only in Wyoming, Thus, while the changes observed in DC are not unprecedented, they were also highly unusual compared to other states and territories.

Changes in birth rates can be a strong function of demographics; for example, if DC had a lower population of women aged 15−44 in 2004−2006 versus 2001−2003, the observed increase in birth rate starting in 2004 might have nothing to do with WLL exposure. When DC DOH trends in reported general fertility rates were examined using the same approach as for Figure 2A, DC general fertility rates were inversely correlated to both incidence of childhood lead poisoning age <1.3 years and median blood lead (SI Figure 2; $R^2 = 0.49$−0.53). Repeating the analysis of Figure 2C for changes in general fertility rates in DC versus both BC and the U.S., revealed the same trend as was observed for the birth rate (SI Figure 3). Thus, changes in demographics do not seem to be a likely explanation for the observed anomalies in DC birth rates.

There was also a reasonable inverse correlation, between DC fertility rates and DC fetal death rates (SI Figure 4; $R^2 = 0.38$). The slope of that curve implies an increase in births of 300 per year when the cases of fetal death are reduced by 30 cases per year, which roughly approximates to the actual data for DC in 2004 versus 2001 when live births increased by 308 and fetal deaths decreased by 34. If this change reflects changes in WLL exposure and its associated effect on spontaneous abortion incidence,[9−12] then decreased fetal deaths account for only about 10% of the observed increase in birth rate and the remaining 90% would be attributed to miscarriages. A ratio of 1 fetal death for every 9 miscarriages was expected based on prior research.[43] Overall, observations in DC are consistent with predictions of higher miscarriage incidence at less than 20 weeks gestation at times with high WLLs and higher maternal lead exposure, which translates to reduced birth rates as expected given the presumed successful use of 19th century lead abortion pills.[9−12]

Revisiting the 1987−1989 USA Today Miscarriage Cluster. A National Institute for Occupational Safety and Health (NIOSH) report summarized a 16 month health hazard investigation for a high profile miscarriage cluster in what was once the USA Today Building complex in Rosslyn, VA.[22] This building receives water from the same source as Washington, DC. A 100% incidence of miscarriages (eight miscarriages for eight pregnancies) was confirmed among women working on two specific floors of one building that underwent renovation during 1988, an activity which was noted to have disturbed the existing copper−lead solder plumbing system to the point that joints failed and "dripping from overhead pipes <was> common."[21] The miscarriages were associated with "working in an area under renovation during the first 20 weeks of pregnancy" (RR = 2.52; 95% CI = 1.43−4.48).[22]

Extensive testing many months after the miscarriages revealed nothing unusual except for very high WLLs (up to 1300 μg/L), with mean lead in first draw drinking water fountain samples of 100 μg/L and mean lead levels after flushing 5 min of 50 μg/L. But the two floors with the renovations and highest incidence of miscarriages had ***anomalously low*** detected WLLs (mean lead of 20 μg/L first draw and 11 μg/L after flushing), WLLs that were 80% lower than in other areas of the building with lower incidence of miscarriages ($p < 0.05$). This finding, coupled with low levels of blood lead for 39 women tested after March 1989, was used to rule out WLLs as a factor contributing to the cluster.[22,23] Expert consensus at the time was that "no matter how much water you would drink here, that by itself would not be sufficient to increase the level of lead in the body of an adult very much at all."[24]

Re evaluation of the NIOSH logic and closer examination of the raw data reveals substantial uncertainty in the conclusions regarding the effect of high WLL. First, recent reports have demonstrated that physical disturbances to pure lead pipe can sometimes create massive water lead spikes over a duration of weeks to months, before eventually improving.[13−16,44] The experimental testing simulating impacts of disturbances during renovations on WLL exposure for occupants on the two floors of the USA Today building conducted for this work, revealed that before the physical disturbance lead release in the two sets of pipes were identical (Figure 3). But after just 30 s of

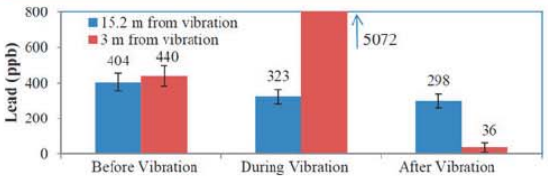

Figure 3. A simulation of construction vibration impacts for the USA Today building, illustrates massive release of lead to water for the month immediately after vibrations, and much lower water lead 2−3 months afterward for disturbed lead pipes.

vibrations at 3 m distance from the pipes, WLL increased over hazardous waste criteria (>5000 μg/L) for cumulative com positive samples collected for the 1 month after the disturbance. Consuming even a small amount of water containing >5000 μg/L lead would greatly exceed the dose from 1900s lead abortion pills. The same vibrations 15 m distant from the pipes had nearly no effect on WLLs (Figure 3). Importantly, three months after the vibration had ceased, the pipes closest to the vibration had 88% *lower* lead release than

more distant pipes not impacted by the vibration ($p < 0.05$), consistent with the notion that removal of a lead rust reservoir during the prior disturbance effectively cleaned out lead from the pipes (Figure 3). Hence, the anomalously low WLLs detected on the two floors with renovation and higher miscarriages in the USA Today building months after the adverse pregnancy outcomes and renovations, is completely consistent with much higher consumer lead exposure on the same floors during the construction.

Further considering that the FOIA revealed the following: (1) only two of the reported low blood lead tests in the NIOSH report were of women on the floors where the miscarriages occurred, (2) more than seven blood lead half lives had passed from the time of the renovation in early 1988 to the time blood lead was drawn, which would have left little trace of a spike in blood lead if it had occurred,[2,45] and (3) WLLs throughout the building are in a range known to be sufficient to cause elevated blood lead and adverse pregnancy outcomes as indicated in this report and elsewhere.[9−13] Hence, the renovation and possible exposure to the high WLLs, was a possible causal factor in the USA Today miscarriage cluster.

■ DISCUSSION

Limitations and Strengths. Inherent limitations to the ecologic study design and the data used in this work, do not allow causal relationships between WLL exposure and adverse pregnancy outcomes to be established. Further research beyond the scope of work presented herein, such as attempting to link addresses of fetal death cases to homes with lead pipe or PSLRs from 2007 to 2009, could increase the strength of the analysis and conclusions associated with this research. Such work was recently called for by an EPA Science Advisory Board, in order to more carefully examine the relationship between PLSRs and incidence of lead poisoning for DC children.[16]

On the other hand, this evaluation also has unique strengths in terms of the following: (1) widespread water lead exposure in a large city with over a half million people, for over a 3 year duration, during a time period when blood lead levels were low by modern standards and influences of other major lead sources such as leaded gas, leaded dust and lead paint were largely under control, (2) presence of a nearby comparison city with similar population and other demographic similarities to eliminate some confounding factors,[18] and (3) availability of over a decade of data synthesizing hundreds of thousands of water lead, blood lead, pregnancy outcomes, and demographic data, collected using modern instrumentation and comparable methods from both cities. The very high statistical power inherent in some aspects of this ecologic study allowed strong temporal associations to be revealed with relatively simple statistical methodology. The observed associations are also consistent with expectations based on a prospective study, which demonstrated that even relatively modest elevations in blood lead (≈5 μg/dL) would increase the likelihood of miscarriage.[11,12]

Ecologic study designs are susceptible to numerous biases and possible confounding factors. At least two are worth noting explicitly herein. First, there is no clear consensus as to the effects of chloramine versus chlorine disinfection on pregnancy outcomes. Early work suggested that a change from chlorine to chloramine would reduce miscarriage rates, whereas several recent studies have indicated that these benefits are not significant, perhaps because certain chloramine disinfection byproducts may be more toxic than previously suspected.[46−49] In Washington, DC., it is clear that hoped for improvements in pregnancy outcomes, which have been cited as a major justification for changing from chlorine to chloramine in 2000,[47] were not realized over the time period of this study. If anything the opposite trend was observed during the time WLLs were elevated. It is also possible that any possible benefits from switching to chloramine after 2000 were overwhelmed by the adverse consequences of very water high lead.

Second, the historical lows in DC fetal death rates during 2004−2006 and 2010−2011 and the rise in birth rates starting in 2004, occurred after or during periods of intense adverse publicity about tap water safety in Washington, DC (Table 1). At these times many consumers were explicitly directed to avoid tap water, use bottled water or install lead filters distributed by the water utility. Because prior research has indicated that avoiding tap water (and using bottled water) can sometimes significantly decrease risk of miscarriages,[50] this factor might confound any attribution of pregnancy outcome trends to WLL exposure alone. However, the strong correlation between maternal blood lead proxies and the measured changes in birth rate, along with the prior research establishing links between modestly elevated blood lead and higher miscarriages, supports the hypothesis that at least some of the improved pregnancy outcomes are due to reduced WLL exposure.

Implications for Policy. From a policy perspective, it is encouraging that most of the data suggest relatively small increases to fetal death rates or reduced birth rates if water was maintained below the 90th% EPA action level of 15 μg/L (Figure 1B), or if public health interventions limit consumer exposure to elevated WLLs when the lead action level was exceeded such as in 2004−2006 or 2010−2011 (Figure 1A; Figure 1C; Table 1). At the same time, the 15 μg/L EPA action level provides little or no safety factor relative to adverse pregnancy outcomes. This point was supported by biokinetic modeling of continuous exposure of 1 year olds to water lead at 7 μg/L, for which 25% of exposed children are predicted to exceed a blood lead level of 5 μg/dL.[51] A one time acute exposure to a single 250 mL glass of water with about 2500 μg/L Pb, was predicted to increase blood lead of a typical 5 year old child from 0 to 5 μg/dL.[51] Because these trends are likely to hold for adults as well, and these types of WLL exposure occur routinely in cities with lead plumbing or after PSLRs,[44,52] public health concern over lead in tap water for pregnant women seems to be justified.[9−13] It is noteworthy that the most recent data has indicated that U.S. fetal death rates have essentially plateaued since 2003 at a level which is higher than for other industrialized countries, and that the reasons for relatively high U.S. fetal death rates are not fully understood and remain a topic of active research.[53,54]

The data presented herein suggest a very high risk for elevated lead (and by extension adverse pregnancy outcomes) in PSLR homes from 2007 to 2009. Brown et al. (2011) reported a 360% increase in lead poisoning incidence for children living in PSLR homes versus typical homes in the city using data collected from 2004 to 2006, and this was when public health protections were in place throughout DC (Table 1). After 2006 the public health protections were removed and the utility stopped collecting water samples after PSLR in consumer homes. Thus, the time period examined by Brown et al. was actually relatively low risk to consumers, compared to the 2007−2009 time period examined in this report. Further support for very high risks after 2006 was obtained during an

analysis of DC DOH Freedom of Information Act (FOIA) data for 2007, which revealed that >12% of cases of lead poisoned children (>5 of 40) lived in DC PSLR homes, even though less than 1% of DC housing units had PSLRs each year.[55] The 2007 FOIA data and that from the CDC through 2006, are also dominated by analysis of children aged 1.5−6 years, whose blood lead levels are generally dominated by lead paint exposure.[2,56] Maternal blood lead can be expected to have a greater proportion of total lead exposure from water than from lead paint when compared to children age 1.5−6 years. For instance, Fertmann et al. (2004) noted that young women reduced their blood lead by 37% if tap water was completely avoided in a city with WLL exposure much lower than in DC PSLR homes.[57] The implication is that very high risk of adverse pregnancy outcomes is possible in the small subset of PSLR homes, providing a practical basis for the spiking fetal death rates in Figure 1C and Table 1 from 2007 to 2009, even when blood lead was declining rapidly and birth rates were increasing throughout the rest of the city.

This work also reinforces the basis for health concerns and warnings associated with lead spikes arising from disturbing old lead plumbing.[3,8,15,44] This evolving knowledge base parallels prior experience with lead paint remediation and renovations, during which careless disturbances created short term lead health hazards that were ultimately regulated.[58] At present there is no requirement to even notify consumers of voluntary PLSR replacements by water utilities, which represent a majority of PLSRs occurring in practice.[16] Implementation of modest health protections for consumers in homes subject to voluntary PLSR including (1) clear notification that their pipe is being disturbed, (2) the fact that serious health hazards may be created for residents, or (3) providing relatively inexpensive (≈$30) water lead filters seems desirable. Indeed, implementa tion of these steps by DC Water in 2010, reinforced by the CDC health alert and heavy media coverage regarding possible health risks from PSLR during public hearings in DC and in Congress,[7,8,17] may have helped to achieve historically low fetal death rates in Washington, DC in 2011 (Table 3). Re examination of the miscarriage cluster in the USA Today building and an associated experiment simulating lead release during renovation, extends the recent concerns with PLSRs to disturbances of lead plumbing within buildings.[44] The same procedures effectively protecting residents in PSLR homes could also be implemented to protect these consumers.

■ ASSOCIATED CONTENT

● Supporting Information

One Table and 4 Figures providing additional analysis on fetal death and birth rates have been developed. This information is available free of charge via the Internet at http://pubs.acs.org/

■ AUTHOR INFORMATION

Corresponding Author

*Phone: (540) 231 7236; fax: (540) 231 7916; e mail: edwardsm@vt.edu.

Notes

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EXHIBIT 8

Maternal Low-Level Lead Exposure and Fetal Growth

Motao Zhu,[1] Edward F. Fitzgerald,[2] Kitty H. Gelberg,[3] Shao Lin,[4] and Charlotte M. Druschel[4]

[1]Department of Community Medicine, West Virginia University, Morgantown, West Virginia, USA; [2]Department of Epidemiology and Biostatistics, State University of New York at Albany, Rensselaer, New York, USA; [3]Bureau of Occupational Health, New York State Department of Health, Troy, New York, USA; [4]Bureau of Environmental and Occupational Epidemiology, New York State Department of Health, Troy, New York, USA

Background: Limited epidemiologic studies have examined the association between maternal low-level lead exposure [blood lead (PbB) < 10 µg/dL] and fetal growth.

Objective: We examined whether maternal low-level lead exposure is associated with decreased fetal growth.

Methods: We linked New York State Heavy Metals Registry records of women who had PbB measurements with birth certificates to identify 43,288 mother–infant pairs in upstate New York in a retrospective cohort study from 2003 through 2005. We used multiple linear regression with fractional polynomials and logistic regression to relate birth weight, preterm delivery, and small for gestational age to PbB levels, adjusting for potential confounders. We used a closed-test procedure to identify the best fractional polynomials for PbB among 44 combinations.

Results: We found a statistically significant association between PbB (square root transformed) and birth weight. Relative to 0 µg/dL, PbBs of 5 and 10 µg/dL were associated with an average of 61-g and 87-g decrease in birth weight, respectively. The adjusted odds ratio for PbBs between 3.1 and 9.9 µg/dL (highest quartile) was 1.04 [95% confidence interval (CI), 0.89–1.22] for preterm delivery and 1.07 (95% CI, 0.93–1.23) for small for gestational age, relative to PbBs ≤ 1 µg/dL (lowest quartile). No clear dose–response trends were evident when all of the quartiles were assessed.

Conclusions: Low-level PbB was associated with a small risk of decreased birth weight with a supralinear dose–response relationship, but was not related to preterm birth or small for gestational age. The results have important implications regarding maternal PbB.

Key words: birth weight, blood lead, epidemiology, fetal growth, low-level lead exposure, pregnancy, preterm birth, small for gestational age. *Environ Health Perspect* 118:1471–1475 (2010). doi:10.1289/ehp.0901561 [Online 21 June 2010]

With the banning of lead-based paint in 1977, and the phasing out of lead-based gasoline in the 1980s and its ban in 1996, the blood lead (PbB) concentration among the general U.S. population has been declining steadily [Centers for Disease Control and Prevention (CDC) 2005]. However, the general population exposure to low lead levels continues because of the widespread use of lead and its ubiquitous nature (CDC 2005). According to the 2003–2004 National Health and Nutrition Examination Survey (CDC 2005), the mean PbB among women 18–49 years of age was 1.2 µg/dL, with a 95th percentile of 2.6 µg/dL.

PbBs < 10 µg/dL induce adverse effects in humans, including elevated blood pressure, impaired nervous system development, delayed sexual maturation, neurobehavioral effects, depressed renal glomerular filtration rate, and reduced heme synthesis [Agency for Toxic Substances and Disease Registry (ATSDR) 2007]. Furthermore, a clear threshold for these sensitive effects has not been identified (ATSDR 2007). Maternal lead can readily cross the placenta and enter fetal blood circulation starting around week 12–14 of pregnancy, making the fetus susceptible to lead poisoning (Lin et al. 1998).

It is biologically plausible that lead can induce low birth weight, preterm birth, and small for gestational age. Lead can potentially impair normal fetal bone growth by competing with calcium for deposition into bone because lead and calcium have similar chemical characteristics (Potula 2005). Experimental evidence provides support for a potential effect of lead on preterm birth. Lead impedes collagen synthesis and praline hydroxylation in mouse, which may have deleterious effects on chorioamniotic membrane structure and induce its premature rupture (Torres-Sanchez et al. 1999). Rats exposed to lead have reduced bone calcium content, reduced trabecular bone volume, altered growth plate morphology, and enhanced activities of spontaneous uterine contraction (Irgens 1998; Torres-Sanchez et al. 1999).

Limited epidemiologic studies have been conducted to examine maternal low-level lead exposure and fetal growth, especially using PbBs (Irgens 1998; Magri et al. 2003; Rothenberg et al. 2002; Sowers 2002; Torres-Sanchez et al. 1999). Some studies included both low-level and high-level lead exposures, restricting the conclusions regarding low-level lead exposure alone (Torres-Sanchez et al. 1999). Other studies are based on convenience samples such as prenatal clinic and Medicaid participants, limiting their generalizability (Sowers 2002).

Our study was designed to help address some of these issues, using a large population-based PbB registry in New York state. The objectives were to examine whether maternal low-level PbB exposure (< 10 µg/dL) was inversely associated with birth weight and directly associated with the risk of preterm birth, and small for gestational age.

Methods

Study population and data sources. The study population comprised upstate New York (New York State, excluding New York City) mothers 15–49 years of age from 2003 through 2005 who had a PbB test before or at the delivery date, and their singleton live births. PbBs were obtained from the New York State Heavy Metals Registry (HMR), which has maintained a statewide database since 1982 and receives reports on exposure to heavy metals, including lead, mercury, arsenic, and cadmium, from physicians and laboratories (New York State Department of Health Bureau of Occupational Health 2008a). In 1992 the reporting requirement was changed from 25 µg/dL to include all test reports regardless of level (New York State Department of Health Bureau of Occupational Health 2008a). Information on birth outcomes and potential confounders was acquired from the birth certificate files, which are maintained by the New York State Department of Health, Bureau of Biometrics.

Study design and data linkage. A retrospective cohort design was used. The existing HMR records were linked with birth certificate files to form the study base. At first, women with multiple PbB reports were identified through deterministic matching techniques and transposed into one record containing information on all reporting dates and PbBs. To minimize the issues of data entry errors or missing values on identifiers, 10 deterministic identifiers were created using

Address correspondence to M. Zhu, West Virginia University, Department of Community Medicine, White Birch Towers, 4th Floor, 1299 Pineview Dr., Morgantown, West Virginia 26505 USA. Telephone: (304) 293-6682. Fax: (304) 293-0265. E-mail: mzhu@hsc.wvu.edu

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components from variables including the case number, social security number, date of birth, first name, last name, telephone number, ZIP code, street address, sex, and street address of the provider or physician ordering test. During each step, 50 matches were randomly selected and reviewed to ensure that the matches were accurate, using all the potential identifying variables: first name, last name, middle name, date of birth, street address, ZIP code, city, state, phone number, sex, street address, name of the provider or physician ordering test, and reporting laboratory identification number. A total of 215,426 women 15–49 years of age were identified from 245,050 PbB tests that reported < 10 µg/dL from 2003 through 2005.

PbB data were then matched with birth certificates to identify women who delivered live infants. Twenty deterministic identifiers were created using components from variables including date of birth, social security number, first name, middle name, last name, phone number, residential street, and ZIP code of the mother, and residential street and ZIP code of the father. A total of 44,932 singleton live births were identified with at least one PbB test by delivery and the maximal lead level < 10 µg/dL. We then excluded records with implausible birth weight–gestational age combinations (Alexander et al. 1996) to reduce the sample size to 44,873. Approximately 3.5% of mothers had multiple singleton births during the 3-year period, and we randomly selected one birth to finalize 43,288 mother–infant pairs. Approximately 3.0% of women received multiple PbB tests, so we similarly selected one test result at random.

This study was approved by the New York State Department of Health and the State University of New York at Albany institutional review boards.

Study variables. **Exposure.** PbB concentration was obtained from the HMR PbB reports. The study level was restricted to < 10 µg/dL, which accounted for 99.2% of reports. Atomic spectrometry is the method for routine screening and diagnostic work (Parsons 1993). Its accuracy is ± 1 µg/dL and the detection limit is 1 µg/dL (Parsons 1993). Any errors in the measurement of PbB would be expected to be nondifferential according to low birth weight and other fetal growth outcomes. Laboratories are required to pass three of the quarterly proficiency tests every year by the New York State Department of Health, Wadsworth Center for Laboratories and Research, to ensure the accuracy and comparability (Lin et al. 1998). The coefficient of variation was approximately 7% among all laboratories in 2005 (New York State Department of Health Wadsworth Center 2006).

Outcomes. Birth outcomes were abstracted from the birth certificate files. Only singleton live births were selected. Birth weight was examined as a continuous variable. Preterm birth was defined as the gestational age < 37 completed weeks from the date of the last menstrual period (March of Dimes Foundation 2007). Small for gestational age was defined as the birth weight below the 10th percentile of birth weight for gestational age based on the distribution of 1996–2000 national birth weight by gestational week from week 25 through week 42 (Boulet et al. 2006). Binary low birth weight (< 2,500 g) was not examined in multiple variable analysis because continuous birth weight provides more statistical power to detect subtle effects. In addition, low birth weight is a mix of preterm, growth-restricted, and constitutionally small births; preterm birth and small for gestational age were examined in this study. Regarding the accuracy of outcomes recorded in New York State birth certificates, the dates of last menses reported in the birth certificate exactly agreed with those recorded in medical records for 87% (Roohan et al. 2003). The agreement rate was increased to 93% when the tolerance was 1 week (Roohan et al. 2003).

Confounders. In addition to the timing of lead test in relation to the date of delivery, various potential confounders were abstracted from the BC files: maternal race (Caucasian, African American, other); maternal ethnicity (Hispanic or not); maternal age at the time of delivery; maternal education (less than high school graduate, high school graduate, some college or college degree, graduate education); participation in financial assistance programs (e.g., Medicaid; Family Health Plus; Women, Infants, and Children; other) (yes or no); self-reported maternal smoking during pregnancy (yes or no); self-reported maternal alcohol consumption during pregnancy (yes or no); self-reported illicit drug use during pregnancy (yes or no); trimester when prenatal care began (first trimester, second trimester, third trimester, or no prenatal care); parity (zero, one, two or more previous live births); sex of child; in wedlock (yes or no); and prepregnancy body mass index.

Statistical analysis. For continuous outcomes (birth weight in grams and gestational age in days), we fitted multiple linear regression with fractional polynomials (Royston et al. 1999). We explored one or two terms of fractional polynomials in term of x^p for PbB, where the power p is from –2, –1, –0.5, 1, 2, 3, and natural logarithmic transformation. The selection of final fractional polynomials

Table 1. Maternal and infant quantitative characteristics, upstate New York, 2003–2005.

Characteristic	*n*	Mean	Selected percentiles						
			Minimum	10th	25th	50th	75th	90th	Maximum
PbB (µg/dL)	43,288	2.1	0	1	1	2	3	3	9.9
Days from lead test to date of birth (day)	43,288	203	0	110	170	204	223	237	1,082
Maternal age (years)	43,288	27.6	15	20	23	27	32	36	49
Body mass index (kg/m^2)	40,797	26.4	12.5	19.9	21.9	24.9	29.4	35.2	66.5
Gestational age (week)	43,288	38.8	20	37	38	39	40	41	44
Birth weight (g)	43,288	3,331	205	2,680	3,030	3,365	3,686	3,997	5,610

Table 2. Maternal and infant qualitative characteristics, upstate New York, 2003–2005 (total *n* = 43,288).

Characteristic	*n*	Percentage[a]
Race		
Caucasian	29,434	68.0
African American	7,113	16.5
Other	6,689	15.5
Missing value	52	
Ethnicity		
Hispanic	8,447	19.7
Missing value	492	
Education		
Less than high school graduate	10,054	23.4
High school graduate	11,675	27.2
Some college or bachelor degree	16,857	39.3
Graduate study	4,337	10.1
Missing value	365	
Smoking		
Yes	8,834	20.5
Missing value	149	
Alcohol drinking		
Yes	493	1.1
Missing value	196	
Drug abuse		
Yes	1,216	2.9
Missing value	973	
Financial assistance program		
Yes	25,803	59.8
Missing value	114	
Start of prenatal care visit		
First trimester	29,187	72.9
Second trimester	8,811	22.0
Third trimester or no prenatal care visit	2,056	5.1
Missing value	3,234	
Parity		
0	17,376	40.4
1	13,715	32.0
2 or more	11,823	27.6
Missing value	374	
In wedlock		
Yes	20,378	47.4
Missing value	261	
Infant sex		
Male	22,154	51.2
Low birth weight		
Yes	2,744	6.3
Preterm birth		
Yes	3,519	8.1
Small for gestational age		
Yes	4,092	9.5
Missing value	112	

[a]The calculation of percentage excluded missing values. There were no missing values for infant sex, low birth weight, and preterm birth.

was based on a closed-test procedure, which maintains the overall type 1 error (alpha level) of 0.05 for tests among 44 different combinations (Royston et al. 1999). For each outcome, a subset of biologically plausible risk factors in addition to PbB was selected to enter the model as potential confounders; those that remained with a significance level of 0.2 were retained (Dales and Urg 1978; Mickey and Greenland 1989; Royston et al. 1999). Fractional polynomials were assessed for continuous confounders including gestational age and maternal age for birth weight outcome. Because the limit of detection for the routine screening and diagnostic laboratory method is 1 µg/dL (Parsons 1993), we conducted sensitivity analysis by *a*) comparing all records; *b*) excluding PbBs of 0 µg/dL; *c*) excluding PbBs < 1 µg/dL.

Furthermore, the quartiles of PbBs (≤ 1 µg/dL; > 1 µg/dL to 2 µg/dL; > 2 µg/dL to 3 µg/dL; > 3 µg/dL to < 10 µg/dL) were used for binary outcomes including preterm birth and small for gestational age. Adjusted odds ratios (aORs) of PbBs were estimated from logistic regression with fractional polynomials (Allison 1999; Royston et al. 1999). The quartiles of PbBs were forced into the model. A closed-test procedure was used to identify the 1 of 44 combinations of one or two fractional polynomials with the best model fit for continuous confounder: maternal age. The criteria for selecting and retaining confounders in the logistic regression were similar to those for linear regression. Analyses were conducted using STATA version 11 (StataCorp, College Station, TX, USA).

Table 3. Association between PbB concentration and birth weight, upstate New York, 2003–2005.

PbB concentration (µg/dL)	Difference in birth weight in grams (model based)[a]	
	Estimate	95% CI
0	Reference	
1	–27.4	–17.1 to –37.8
2	–38.8	–24.1 to –53.4
3	–47.5	–29.6 to –65.4
4	–54.8	–34.2 to –75.5
5	–61.3	–38.2 to –84.4
6	–67.2	–41.8 to –92.5
7	–72.5	–45.2 to –99.9
8	–77.6	–48.3 to –106.8
9	–82.3	–51.2 to –113.3
10	–86.7	–54.0 to –119.4

[a]The model was a linear regression with fractional polynomials after adjustment for timing of lead test, gestational age, maternal age, race, Hispanic ethnicity, education, smoking, alcohol drinking, drug abuse, in wedlock, participation in special financial assistant program, parity, and infant sex. PbB concentration was transformed using a square root. The coefficient was –27.4 with an SE of 5.3.

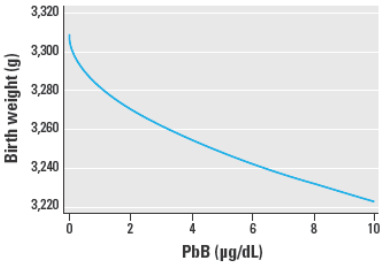

Figure 1. Model-based dose–response relationship.

Results

The average PbB concentration was 2.1 µg/dL, and the median was 2 µg/dL (Table 1). The average number of days from lead test to delivery was 203, and the 90th percentile was 237. Most PbB tests were conducted between the date of last menses and the date of delivery. The average birth weight was 3,331 g, and gestational age was 38.8 weeks. Table 2 presents the distribution of selected categorical maternal and infant characteristics. Approximately 68% of births were to white women, and Hispanics accounted for 20%. The rates of low birth weight, preterm birth, and small for gestational age were 6.3%, 8.1%, and 9.5%, respectively.

A model that assumed a linear relation between the square root of PbB and birth weight fit the data better than models with all other combinations of fractional polynomial terms evaluated. Consequently, our final model included only a single term for PbB (raised to the 0.5 power), with an adjusted coefficient of –27.4 [95% confidence interval (CI), –37.7 to –17.1]. Estimated changes in birth weight with a 1-µg/dL change in PbB varied across the PbB distribution in the study population, consistent with the supralinear shape of the dose–response curve dictated by the model, so that a 1-µg/dL change in PbB from 0 µg/dL to 1 µg/dL was associated with a 27.4-g decrease in mean birth weight, whereas a 1-µg/dL change in PbB from 9 µg/dL to 10 µg/dL was associated with a 4.4-g decrease in mean birth weight (from a predicted mean decrease relative to predicted mean birth weight when PbB = 0 of 82.3 g to 86.7 g) (Table 3). Therefore, the model predicts the strongest estimated effects at the lowest levels of exposure, without a lower threshold of PbB below which there would be no predicted effect on birth weight. Figure 1 displays this dose–response relationship.

As for sensitivity analysis, the best-fit fractional polynomials were PbB^{-1} + PbB^{-1} × logarithmic-transformed PbB, after excluding PbB of 0 µg/dL from analysis (data not shown). Compared with PbB of 0.5 µg/dL, PbB of 9.5 µg/dL was associated with a 51-g decrease in birth weight. Compared with PbB of 1 µg/dL, PbB of 10 µg/dL was associated with a 32-g decrease in birth weight. When PbBs < 1 µg/dL were excluded, untransformed PbB fit the data the best, and the linear regression coefficient was a 7.0-g decrease in birth weight for a 1-µg/dL increase in PbB. Therefore, PbB of 10 µg/dL was associated with a 63-g decrease in birth weight, relative to PbB of 1 µg/dL. In contrast, the analysis using all PbBs including zeros and < 1 µg/dL suggested that PbB of 9.5 µg/dL was associated with an 84-g decrease in birth weight, relative to PbB of 0.5 µg/dL, and that PbB of 10 µg/dL was associated with a 59-g decrease in birth weight, relative to PbB of 1 µg/dL. The analysis with all PbBs provided robust estimated effects of lead on birth weight.

A model that assumed a linear relation between untransformed PbB and gestational age in days fit the data better than models with all other combinations of fractional polynomial terms evaluated. Consequently, our final model included only a single linear term for PbB, with an adjusted coefficient of –0.09 (95% CI, –0.24 to 0.05) after adjustment for timing of lead test, maternal age, race, smoking, alcohol consumption, participation in special financial assistance program, parity, and infant sex (data not shown).

Table 4 presents the association between the quartile PbBs and dichotomous outcomes: preterm birth and small for gestational age. There were not clear dose–response trends when all quartiles were assessed. The aORs for PbBs between 3.1 and 9.9 µg/dL (highest quartile) was 1.04 (95% CI, 0.89–1.22) for preterm birth and 1.07 (95% CI, 0.93–1.23) for small for gestational age, relative to ≤ 1 µg/dL (lowest quartile).

Table 4. Association between maternal PbB level and preterm birth, and small for gestational age, upstate New York, 2003–2005.

Maternal PbB level	Preterm birth			Small for gestational age		
	Cases (*n*)	aOR[a]	95% CI	Cases (*n*)	aOR[b]	95% CI
≤ 1.0	1,069	1.00	Reference	1,168	1.00	Reference
1.1–2.0	1,036	1.03	0.93–1.13	1,268	1.07	0.98–1.17
2.1–3.0	1,171	1.01	0.92–1.10	1,353	1.06	0.98–1.16
3.1–9.9	243	1.04	0.89–1.22	303	1.07	0.93–1.23

[a]aORs are estimated from logistic regression with fractional polynomials after adjustment for timing of lead test, maternal age at delivery, race, Hispanic ethnicity, smoking, drug abuse, in wedlock, participation in special financial assistance program, parity, and infant sex. The quartiles of PbB concentration were untransformed, and fractional polynomials were used for maternal age. [b]aORs are estimated from logistic regression with fractional polynomials after adjustment for timing of lead test, maternal age at delivery, race, education, smoking, drug abuse, in wedlock, participation in special financial assistance program, parity, and infant sex. The quartiles of PbB concentration were untransformed and fractional polynomials were assessed for maternal age.

Discussion

Overall, maternal PbBs < 10 µg/dL were associated with a small but statistically significant decrease in birth weight. The decrease in birth weight for a 1-µg/dL increase in PbB ranged from an estimated means value of 4 g (from 9 to 10 µg/dL) to 27 g (from 0 to 1 µg/dL). This is consistent with the estimate of a 6.2-g decrease in birth weight per 1-µg/dL increase in PbB from a study of 272 mother–infant pairs in Mexico (Gonzalez-Cossio et al. 1997); 3.0 g in a study of 4,354 pregnancies in Boston (Bellinger et al. 1991); 0.8 g from a study of 54 term neonates in Turkey (Atabek et al. 2007); and 0.3 g in a study of 55 newborns in Brazil (Zentner et al. 2006), despite that fact that their mean lead levels were higher than ours.

We found that a model of birth weight as a function of square root–transformed PbB provided the best fit to the data. This model predicted estimated effects of lead that were greater at the lower end of the PbB distribution than at higher levels (supralinear dose–response relationship). A similar supralinear relationship has been reported for PbB < 10 µg/dL with IQ and Mental Development Index (Canfield et al. 2003; Lanphear et al. 2005; Tellez-Rojo et al. 2006). A pooled analysis of seven international prospective cohort studies found that the decrease in full-scale IQ score per 1-µg/dL increase in PbB estimated from the linear regression with untransformed PbB was greater among children with a maximum PbB < 7.5 µg/dL than in those with a maximum PbB ≥ 7.5 µg/dL (Lanphear et al. 2005). Further analysis suggested a linear relationship between the logarithmic-transformed PbB and IQ (coefficient: 6.9) (Lanphear et al. 2005). An analysis of 294 children found a logarithmic-transformed PbB was linearly associated with Mental Development Index (Tellez-Rojo et al. 2006). The estimated effect of lead estimated from the linear regression with untransformed PbB was larger at < 5 µg/dL than between 5 and 10 µg/dL (Tellez-Rojo et al. 2006). Researchers have used quadratic term (Canfield et al. 2003) and logarithmic transformations (Lanphear et al. 2005; Tellez-Rojo et al. 2006) to describe the supralinear relationship between lead and intellectual impairment. We found that the square root transformation provided the best fit for birth weight, compared with 43 other fractional polynomials linear, reciprocal, logarithmic, square foot, quadratic, and cubic terms. Further studies are needed to confirm whether the supralinear relationship between PbB and birth weight is best described with a square root transformation. Consistent with previous studies of intellectual development (Canfield et al. 2003; Lanphear et al. 2005; Tellez-Rojo et al. 2006), our analysis supports that there is no clear threshold for the effects of lead on sensitive outcomes such as birth weight.

Bellinger et al. reported that the mean gestational age was 0.3 week longer among those with umbilical cord PbBs 5.0–9.9 µg/dL, relative to PbBs < 5.0 µg/dL (Bellinger et al. 1991). In contrast, we found that a 1-µg/dL increase in maternal PbB was associated with a statistically nonsignificant 0.09-day decrease in gestational age. Similarly, Jelliffe-Pawlowski et al. reported that among women with PbB ≥ 10 µg/dL, a 1-µg/dL increase in lead level was associated with an average 0.3-day decrease in gestational age (Jelliffe-Pawlowski et al. 2006). In a case–control study of 620 pregnant women in Mexico City, compared with umbilical cord PbBs < 5.1 µg/dL, the aOR of preterm birth for lead level 5.1–9.0 µg/dL was 2.72 (95% CI, 1.03–7.19) among primiparous women, but 0.48 (95% CI, 0.21–1.08) among multiparous women (Torres-Sanchez et al. 1999).

Bellinger et al. found that lead levels between 5 and 9.9 µg/dL were not statistically related to increased risk in dichotomous preterm birth and small for gestational age, compared with lead levels < 5 µg/dL (Bellinger et al. 1991). A cohort study by Sowers (2002) of 705 pregnant women in Camden, New Jersey, did not find any statistically significant association with dichotomous preterm birth, or small for gestational age. Consistent with their study, our study did not find statistically significant associations.

Jelliffe-Pawlowski et al. reported that women with PbBs ≥ 10 µg/dL were approximately three times as likely to experience a preterm delivery as women with lead levels < 10 µg/dL (aOR = 3.2; 95% CI, 1.2–7.4) and that their risk of having a small-for-gestational-age infant was more than four times that of women with lead levels < 10 µg/dL (aOR = 4.2; 95% CI, 1.3–13.9) (Jelliffe-Pawlowski et al. 2006). Chen et al. (2006), in a study of 1,611 mother–infant pairs in Taiwan, China, suggested that maternal PbBs of ≥ 10 µg/dL were related to a doubling risk in low birth weight, preterm birth, and small for gestational age compared with maternal PbBs < 10 µg/dL. Highly elevated maternal PbBs would be expected to have adverse effects on fetal growth.

This study has multiple strengths. For example, we used PbBs to measure the absorbed dose circulated in the blood through various exposure routes and sources for pregnant women, which is more accurate than occupation history and other proxy exposure measures. By restricting the lead concentrations to < 10 µg/dL, the associations between maternal lead level and fetal growth found in this study were not influenced by lead concentrations > 10 µg/dL, unlike previous studies that included lead concentrations below and > 10 µg/dL. Because this study was based on a statewide registry and the study lead concentration was close to the lead distribution among the general population, findings should be more generalizable than those based on occupational settings or convenience samples. Furthermore, this study had a large sample size to detect subtle effects.

A possible limitation is selection bias. We found that the mothers in this study were younger and less likely to be Caucasian than other mothers in upstate New York. The linkage rate of PbB reports with birth certificates was higher for mothers 18–19 years of age, African Americans, and with low-weight births, consistent with the selective screening for pregnant women at risk for adverse pregnancy outcome or lead exposure.

Dietary calcium and multiple vitamin use during pregnancy could not be controlled, as they were not collected on either the birth certificates or the HMR. Low dietary calcium intake may increase the gastrointestinal absorption of lead (Bogden et al. 1995). Calcium supplementation may reduce the lead mobilization from bone during pregnancy and therefore reduce the potential lead toxicity (Bellinger 2005; Han et al. 2000). Furthermore, residual confounding may exist because of the potential misclassification or categorization of confounders. For example, maternal smoking was recorded as "yes or no" in birth certificates. Its sensitivity was 89% and specificity was 99% using medical records as a gold standard (Roohan et al. 2003). There was no detailed information on the duration and frequency of smoking.

The results of this study have important implications regarding the recommended action level for childhood PbB. Although 10 µg/dL is the current reference level set by the CDC (ATSDR 2007), this study suggests that maternal PbBs < 10 µg/dL may affect fetal growth. This issue is of public health significance; in 2005, the HMR received about 84,000 reports on women in New York state with PbBs < 10 µg/dL, and most of the reports were regarding women of reproductive age. Our study supports the continuation of lead screening during pregnancy, especially among women who are at risk because of current high-dose exposure, which is recommended by the New York State Department of Health (New York State Department of Health Bureau of Occupational Health 2008b).

Conclusion

Among pregnant women whose PbB was < 10 µg/dL, PbB (square root transformed) was inversely associated with birth weight. Such findings suggest that the decrease in birth weight per 1-µg/dL increase in PbB was greater at lower concentrations than at higher

concentrations without evidence of a lower threshold of effect. These results are important, given the high prevalence of low-level lead exposure among pregnant women and the controversy regarding the recommended action level for maternal PbB.

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EXHIBIT 9

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Blood Lead Levels Measured Prospectively and Risk of Spontaneous Abortion

Victor H. Borja-Aburto,[1,4] Irva Hertz-Picciotto,[2] Magdalena Rojas Lopez,[1] Paulina Farias,[1] Camilo Rios,[3] and Julia Blanco[1]

Studies of low to moderate level lead exposures have reported mixed findings regarding the risk of spontaneous abortion, despite lead's abortifacient properties at very high doses. To evaluate the risk of spontaneous abortion from low or moderate lead exposures, a nested case-control study was conducted within a cohort of pregnant women in Mexico City, 1994–1996. During their first trimester, 668 women enrolled, were interviewed, and contributed blood specimens. Pregnancies were followed by home visits or telephone calls. Spontaneous abortions before week 21 ($n = 35$) were matched with pregnancies that survived beyond week 20 ($n = 60$) on maternal age, hospital, date of enrollment, and gestational age at enrollment. Mean blood lead levels were 12.03 μg/dL for cases and 10.09 μg/dL for controls ($p = 0.02$). Odds ratios for spontaneous abortion comparing 5–9, 10–14, and ≥15 μg/dL with the referent category of <5 μg/dL of blood lead were 2.3, 5.4, and 12.2, respectively, demonstrating a significant trend ($p = 0.03$). After multivariate adjustment, the odds ratio for spontaneous abortion was 1.8 (95% confidence interval = 1.1, 3.1) for every 5 μg/dL increase in blood lead. Low to moderate lead exposures may increase the risk for spontaneous abortion at exposures comparable to US general population levels during the 1970s and to many populations worldwide today; these are far lower than exposures encountered in some occupations. *Am J Epidemiol* 1999;150:590–7.

abortion; blood; lead; lead poisoning; pregnancy outcome

Adverse effects of lead on the nervous system at both high and low doses, and on the hematopoietic, renal, and reproductive systems at high doses, are well known (1). Neurodevelopmental effects from prenatal and early childhood exposures have been observed at relatively low levels of lead and may be the most sensitive endpoint for lead toxicity (2–5).

Although fetuses of exposed pregnant women are considered to be at particularly high risk for certain effects of lead (6), the specific actions of this metal in the prenatal period are not well understood, nor is it clear what the risks are at low levels of exposure. Some evidence suggests that, during pregnancy, stores of lead deposited in bone over the lifetime may be mobilized, particularly in women who smoke (7) or in women whose calcium intake is low (8). Lead has long been known to diffuse readily across the placenta (9, 10).

In the early part of this century, reports of pregnant women occupationally exposed to high levels of lead in England, Hungary, and elsewhere described increases in spontaneous abortions, stillbirths, premature births, and neonatal deaths, compared with mothers in non-exposed occupations (11). Studies at lower exposures have found inconsistent associations with birth weight and prematurity (12). A higher incidence of spontaneous abortion was observed among women who themselves had suffered from childhood lead poisoning (13), but only a few studies have examined spontaneous abortions in relation to lower levels of lead, e.g., those encountered in the general population in many urban areas of the world. The findings have been mixed, with some studies suggesting an association (14–15) and others showing none (16–19). Methodological problems in these studies, mainly in regard to the assessment of exposure, hamper interpretation. In particular, exposure assessment relied on questionnaires (18, 19), on measurements taken after the abortion occurred (14) or later in pregnancy for non-cases than for cases (15, 16), or on ecologic classification based on residence at a later time point (after the pregnancy in question) (17, 18). For

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Abbreviations: ANOVA, analysis of variance; CI, confidence interval; OR, odds ratio; VDT, video display terminal.

[1] Instituto Nacional de Salud Publica, Cuernavaca, Morelos, Mexico.
[2] University of North Carolina, Chapel Hill, NC.
[3] Instituto Nacional de Neurología y Neurocirugía, Manuel Velasco Suarez, Mexico City, Mexico.
[4] Currently at Centro Nacional de Salud Ambiental, Metepec, Mexico.
Reprint requests to Dr. Irva Hertz-Picciotto, Department of Epidemiology, CB #7400, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599.

most of these investigations, spontaneous abortion was not the primary outcome of interest, and several studies involved very small numbers of cases (13, 15, 16).

In light of the inconclusive evidence from previous reports and their methodological deficiencies, this investigation was conducted to evaluate if currently observed levels of lead increased the risk of spontaneous abortion in pregnant women of Mexico City. Environmental sources of lead exposure in Mexico City include lead-glazed ceramic cookware and leaded gasoline (20). The design of the study ensured 1) measurement of blood lead early in pregnancy and 2) prospective ascertainment of pregnancy losses after the date of blood draw.

MATERIALS AND METHODS

A nested case-control design was carried out within a cohort of 668 pregnant women seeking pregnancy diagnosis or prenatal care in 13 private and public hospitals in Mexico City. Women were recruited during the first 12 weeks of gestation at their first visit to the clinic. All of the pregnancies were confirmed with urine human chorionic gonadotropin (hCG) and/or ultrasound. Informed consent procedures were approved by the institutional review board at the Instituto Nacional de Salud Publica. After informed consent was acquired, blood specimens were obtained, and a questionnaire administered. The questions addressed sources of lead; nutritional factors that could influence absorption or toxicity of lead; sociodemographic, occupational, and life-style factors; drugs used; and reproductive and medical histories of the women. The blood specimens were used for measurement of lead and also of serum antibodies against infectious agents potentially associated with pregnancy loss.

Each woman was regularly contacted, once every 2 weeks, either by telephone (83 percent) or by means of home visits by trained study personnel (17 percent) when telephone calls were not possible, to determine the status of her pregnancy through week 20 of gestation. For two of the cases, the cooperating physicians from the private clinics also informed us of spontaneous abortions among their patients. For each woman who had a spontaneous abortion, defined as a pregnancy loss by week 20 of gestation, two controls were randomly selected from women with normal pregnancies at the time that the case occurred, with matching on maternal age (±2 years), the calendar date and gestational age at which the first blood sample was drawn (±2 weeks), and the type of clinic (private vs. public). The monitoring of controls continued through week 20 of gestation, to ensure that they did not have an abortion. For some of the women, only one control was identified that satisfied the matching criteria.

For women recruited from private clinics, the questionnaires were self-administered, whereas for women from the public clinics, the interviews were carried out through in-person interviews, because some of these women could not read or write. This strategy ensured that the method of interview was the same within each matched set.

When blood was drawn for pregnancy diagnosis or clinical purposes, a sample was also collected for this study. Blood was drawn from the antecubital vein through a vacutainer system to prevent atmospheric contamination. For lead measurements, blood was collected in lead-free plastic tubes containing EDTA as anticoagulant. Within 2 hours, these were transported to the laboratory in cold packs, and then stored refrigerated at 5°C. A second tube was collected and centrifuged and the sera specimens were frozen and stored for later analyses among cases and controls.

Blood lead determinations were carried out in duplicate using atomic absorption spectrophotometry with a graphite furnace (21). These analyses were conducted at the Laboratorio de Neuroquimica at the Instituto Nacional de Neurología y Neurocirugía in Mexico City. This laboratory participates in the blood lead proficiency testing program of the US Centers for Disease Control and Prevention in Atlanta, Georgia. The coefficient of variation for duplicate samples was 4.8 percent. With each batch of samples, one method blank, one spiked sample, and one duplicate sample are routinely analyzed. Calibration verification was performed after each batch of samples.

For the determination of maternal infections, sera samples were transported to the Laboratorio de Referencia Sociedad Anonima (Mexico City) where assays were carried out for immunoglobulins against toxoplasma, rubeola, cytomegalovirus, herpes type 1, herpes type 2, chlamydia, and syphilis. The following kits were used: Toxotest HAI (Weiner Laboratories, Argentina) for immunoglobulin M (IgM) against toxoplasma; enzyme-linked immunoadsorbent assay (ELISA) (GULL Laboratories, Salt Lake City, Utah) for IgM against rubeola, cytomegalovirus, and herpes types 1 and 2; enzyme immunoassay (EIA) (GULL Laboratories) for immunoglobulin G against chlamydia; and venereal disease research laboratory (VDRL) test (Wiener Laboratories, Argentina) to detect antibodies against *Treponema pallidum*. The sera specimens for these assays were kept frozen up to 6 months until analyzed.

The information from the questionnaires and samples was captured electronically using double entry, checked for range and consistency, and corrected. Descriptive analyses were conducted on all variables. Crude (unadjusted) analyses included both a compari-

son of mean blood lead level in cases to that in controls using two-way analysis of variance (ANOVA), and the calculation of a matched sets odds ratio using the McNemar method (22). (These methods allow for varying numbers of controls per case.) Blood lead was analyzed as a categorical variable using 5 μg/dL increments (<5, 5–9, 10–14, ≥15 μg/dL) in order to assess whether the basic assumption of logistic regression, namely that the logit (the logarithm of the odds of disease) increases linearly with exposure, was violated. As the data supported this assumption, further analyses used a continuous variable for blood lead.

To control for confounding, conditional logistic regression models were fit, in which each stratum consisted of a spontaneous abortion case and its matched control(s). Model-building proceeded stepwise by forward selection. Potential confounders were: medical conditions (toxoplasmosis, diabetes, thyroid disorder and hypertension); reproductive characteristics (gravidity, previous spontaneous abortion, menstrual irregularity, age at first sexual contact, previous C-section and spermicide use as last method of contraception); sociodemographic variables (age, education); and lifestyle factors (active and passive smoking, coffee consumption, alcohol consumption, calcium supplementation during pregnancy, use of hair dye, video display terminal (VDT) exposure, and unusual physical exertion). These were evaluated for inclusion in the model by checking changes in the estimated odds ratio for lead and spontaneous abortion (23). We also retained variables that were predictive of spontaneous abortion ($p < 0.10$), or that are established risk factors on which we did not match.

RESULTS

The cohort included 668 women recruited between January 1994 and June 1996, 202 from private hospitals and 466 from public hospitals (table 1). Their age ranged from 14 to 43 years, with a mean of 27 years. On average, these women were recruited in gestational week 9 (dated from the first day of their last menstrual period). The women had an average blood lead level at enrollment of 11.03 μg/dL, almost identical to the initial findings from a subset of the cohort (20). Loss to follow-up (moved and could not be located or never returned to the clinic or gynecologist) by week 20 was 15.8 percent, and was similar for private versus public clinic patients.

Of the 562 women who were successfully followed to week 20, a total of 36 women experienced a spontaneous abortion, for a crude risk of 6.4 percent. One of these cases experienced an accident and was excluded from further analyses. For the remaining 35 cases, a total of 60 controls were identified, that is, two controls for each of 25 cases, and one control for each of 10 cases. Most of the abortions occurred before week 12.

TABLE 1. General characteristics of the cohort of pregnant women: case-control study of blood lead levels and spontaneous abortion, Mexico City, 1994–1996

Variable	No.	%
Clinic type (n = 668)		
Private	202	30.2
Public	466	69.8
Pregnancies (n = 668)		
1st pregnancy	301	45.1
≥2nd pregnancy	367	54.9
Gestational age at entry (weeks) (n = 668)		
4–6	116	17.4
7–9	311	46.5
10–12	241	36.1
Gestational age at pregnancy losses (weeks) (n = 35)		
7–9	13	37.1
10–12	8	22.9
13–15	7	20.0
16–18	5	14.3
19–20	0	0.0
Unknown	2	5.7

Table 2 compares cases and controls with respect to continuous variables, including sociodemographic and other factors. No differences were seen for age, self-reported education, per capita income, or age at first sexual contact. However, compared with the controls, the cases reported spending time near a greater number of smokers at their homes and workplaces. Table 3 compares cases and controls for dichomotous factors. Cases were more likely to report menstrual irregularity, a previous cesarean section, a previous spontaneous abortion, spermicide use as the last method to avoid pregnancy, working with VDTs, and alcohol

TABLE 2. Comparison of cases and controls on selected variables: case-control study of blood lead levels and spontaneous abortion, Mexico City, 1994–1996

Variable	Cases (n = 35)	Controls (n = 60)	p value*
Maternal age (years)	28 (16–40)†	28 (16–40)	0.85
Education (no. of completed years)	12 (6–17)	10 (3–17)	0.78
Gestational age at entry (weeks)	8 (4–10)	8 (4–12)	0.72
Age (years) at first sexual contact	22 (13–34)	19 (13–30)	0.11
No. of cigarettes smoked during pregnancy (for smokers only)	1 (1–10)	3 (2–5)	0.12
No. of persons who smoke nearby	1 (0–20)	1 (0–5)	0.10

* p value by Kolmogorov-Smirnov test. However, all variables were examined for confounding in the multivariate model, using the change-in-estimate criterion.

† Median value (range) throughout table.

TABLE 3. Paired odds ratios of binary exposures for spontaneous abortion: case-control study of blood lead levels and spontaneous abortion, Mexico City, 1994–1996

Variable	Cases (n = 35)		Controls (n = 60)		Odds ratio*	95% CI†
	No.	%	No.	%		
Reproductive factors						
Menstrual irregularity	12	34	13	22	2.1	0.65, 6.7
Primigravida	21	60	28	47	2.8	0.85, 9.0
Previous spontaneous abortion	5	14	3	5	2.2	0.51, 9.3
Previous cesarean section	8	23	3	5	4.0	1.0, 15.3
Spermicide use‡	3	9	2	3	3.0	0.50, 18.0
Life-style/occupational						
Smoker	4	11	10	17	0.62	0.19, 2.1
Coffee consumption	10	29	15	25	1.2	0.42, 3.5
Alcohol consumption§	3	9	1	2	5.6	0.62, 57.7
Calcium supplementation during pregnancy	6	17	27	45	1.6	0.41, 6.3
Dyed hair	6	17	9	15	1.1	0.34, 3.9
Video display terminal exposure	6	17	2	3	5.2	1.0, 25.9
Unusual physical exertion	12	34	18	30	1.2	0.46, 3.0
Medical factors						
Chronic conditions¶	9	26	14	23	1.1	0.42, 2.7
Serum positive for toxoplasmosis	2	6	1	2	3.6	0.36, 44.1

* The matched set odds ratio is calculated using discordant sets and cannot be directly obtained from the first two columns of the table.
† CI, confidence interval.
‡ As the last method of birth control used.
§ More than one glass a week of wine, beer, or liquor.
¶ Includes diabetes mellitus, hypertension, and thyroid disorder.

consumption more than once a week, although for all of these risk factors, the numbers of exposed subjects were small. Confidence intervals included the null value, except for previous cesarean section and VDT exposure. Cases were more frequent in primigravidas. None of the cases or controls were positive for current infection of rubeola, cytomegalovirus, herpes type 1, herpes type 2, chlamydia, or syphilis. Two cases and one control were positive for toxoplasmosis.

The mean blood lead level of cases was 12.0 μg/dL (range 3.1–29 μg/dL) and of controls, 10.1 μg/dL (range 1.3–26 μg/dL). The two-way ANOVA test to take into account multiple controls per case yielded an F statistic of 5.61 ($p = 0.021$). The risk for spontaneous abortion showed a monotonic rise with increases in blood lead. Compared with the reference category of <5 μg/dL of blood lead, women whose blood lead levels were 5–9, 10–14, and ≥15 μg/dL had increasingly greater risks for spontaneous abortion: odds ratios (based on matched sets) were 2.3, 5.4, and 12.2, respectively (test for trend, $p = 0.03$). Graphical inspection of logits, or equivalently, odds ratios plotted on a logarithmic scale (figure 1), indicates that the assumption of linearity was met; hence further analyses used blood lead as a continuous variable.

In a multiple conditional logistic regression model predicting a spontaneous pregnancy loss by week 20, the only retained variables were a previous spontaneous abortion (an established risk factor) and blood lead level. Matching factors were included in the initial models but the matching was apparently quite effective, as none of these factors was predictive of the outcome nor did any factor confound the association between lead and spontaneous abortion. Similarly, age, education, life-style, and medical conditions also were not confounders, i.e., adjustment for them did not alter the estimated odds ratio for the association of lead and spontaneous abortion. Thus, the final model is shown in table 4.

The risk of spontaneously aborting the current pregnancy increased 2.5-fold (95 percent confidence interval (CI) 0.53, 11.7) for women with a history of a spontaneous abortion. For each 1 μg/dL increase in blood lead, the risk increased 1.13-fold; this magnitude of association represents close to a doubling of spontaneous abortion risk for every 5 μg/dL increase in blood lead (odds ratio (OR) = 1.8, 95 percent CI 1.1, 3.1).

DISCUSSION

This study provides evidence that blood lead levels once considered moderate may be associated with an increased risk of spontaneous abortion. Many decades ago, elevated rates of fetal loss of fivefold and higher

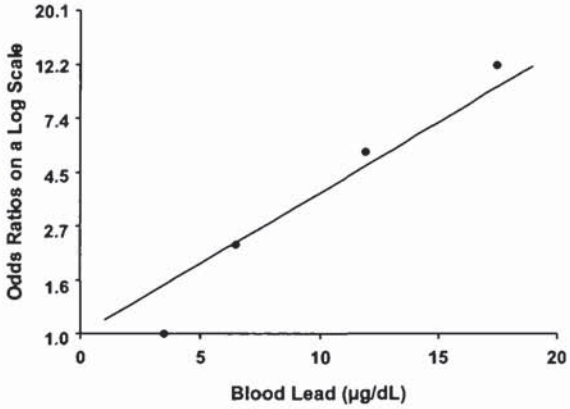

FIGURE 1. Spontaneous abortions versus blood lead level in Mexico City, 1994–1996. Odds ratios are plotted on a logarithmic scale in relation to blood lead, measured both continuously and categorically. The points are calculated from a conditional logistic regression model with three indicator variables, comparing blood lead in the ranges of 5 to <10, 10 to <15, and ≥15 µg/dL with blood lead <5 µg/dL; they are plotted at the median blood lead level in each category. The plotted line is based on the model with blood lead as a continuous variable (fitted model shown in table 4), which assumes that an odds ratio of 1.0 corresponds to a blood lead concentration of zero. The graph allows visual inspection to assess the assumption of linear logits with increasing blood lead. Because this assumption is reasonably well met by the data, the use of a model with the continuous variable for blood lead is supported.

TABLE 4. Final model—multivariate adjusted* odds ratios and 95% confidence intervals (CI) for spontaneous abortion: case-control study of blood lead levels and spontaneous abortion, Mexico City, 1994–1996

Variable	Coefficient	Odds ratio	95% CI	*p* value
Blood lead (per 1 µg/dL)	0.12	1.13	1.01, 1.3	0.03
Previous spontaneous abortion (yes:no)	0.92	2.5	0.53, 11.7	0.25

* Based on a conditional logistic regression model.

were observed in occupationally exposed women at high doses (11, 24). The levels of lead in blood in the women in this study are all below the acceptable standard for occupational exposures. Although the number of cases is relatively small, the associations are statistically significant and demonstrate a clear monotonic dose-response across four levels of exposure. We consider the biologic plausibility of these findings and the strengths and limitations of the study.

There is a growing literature on the endocrine disruptive properties of lead in males and females which can explain failures to conceive (25–28). However, the mechanisms for losses after implantation, as observed in this study, of recognized and confirmed pregnancies, are not totally clear. Possible mechanisms include preconceptional effects on gametogenesis in both males and females, impairment of the hormonal environment needed to maintain pregnancy, and direct teratogenic effects on the fetus.

Paternal exposure to lead may be related to spontaneous abortions by three pathways: 1) lead in the father is passed through semen to the mother; 2) lead in the father's work clothes, equipment, hands, etc., is a source of exposure for the mother; 3) lead burden in the father alters his sperm. The first scenario would not necessarily result in elevated maternal blood lead, while the second would likely have such an effect and could have been operating in our study subjects. As for sperm alterations, studies of exposed workers in Romania (29) and Southern Italy (30) showed alterations in sperm cytology without perturbation of the hypothalamic-pituitary system, suggesting a direct toxic effect on sperm production and transport. Other work suggests the potential impact of pre- or periconception paternal exposures on later events in pregnancy (31). In the current study, a direct effect of paternal exposure cannot be ruled out, because such exposure was assessed only indirectly (by maternal questionnaire) and neither blood lead levels nor sperm or semen parameters were measured. However, only nine participants (three cases and six controls) reported that their partner was occupationally exposed.

Experimental evidence supports effects of lead on female reproductive function both at high and moderate levels. In pregnant rodents administered lead at moderate doses (achieving 10–40 µg/dL in blood), serum progesterone levels were reduced in dams, and hypothalamic levels of gonadotropin-releasing hormone (GnRH) and somatostatin were suppressed in both dams and fetuses (32). In female monkeys, lead intoxication at high doses causes degeneration of ovarian follicles (33). Lead is also a demonstrated teratogen in rats, causing congenital malformations (34). Human cytogenetic studies in both males and females with occupational exposure suggest that lead increases the rate of chromosomal aberrations in cultured lymphocytes (35, 36).

Our study has several strengths not found in previous investigations of reproductive effects in populations exposed environmentally to lead. Blood lead levels were measured early in pregnancy and prior to the spontaneous abortion; information on spontaneous abortions was collected prospectively; and important potential confounders were efficiently controlled through matching and the corresponding matched analysis. Each of these features added to the validity of our findings.

Olsen and Skov (38) recommend that in a case-control study, the controls should be pregnant women

sampled from the same population at risk and matched for gestational age at enrollment so that the time window during which any exposure can occur is the same in both groups. Our design followed this recommendation. Because blood lead levels (6) and the risk of spontaneous abortion (37) both change as pregnancy progresses, an inappropriate timing of lead measurement in terms of gestational age could either mask an association or create an artifactual one. The measurement of blood lead levels prior to the event of interest is important to assure a nonspurious association. None of the previous studies were designed to address these issues.

A further strength of our study was the substantial range of exposures, from 1.4 to 29 μg/dL. Prior studies with a smaller range would have had lower statistical power (39).

In this study, we matched on gestational age at entry measured since the last menstrual period. However, if lead causes menstrual irregularities at the higher doses observed in this study, bias could be present. The gestational age at entry could be an overestimate of true gestational age for these women, because their interval between last menses and the conceptive ovulation could have been longer. This scenario would imply a shorter time-since-conception when they entered the study, and hence a higher cumulative probability of spontaneously aborting between entry into the study and week 20; thus, the women who are more highly exposed would be overrepresented among cases, leading to an overestimate of the association, if any, with spontaneous abortion.

Another potential source of upward bias would be present if problem pregnancies are characterized by a smaller or delayed increase in fluid volume. A lack of the normal increase in blood volume leading to a less viable pregnancy would be associated with the appearance of increased blood lead concentrations. However, fluid volume does not begin to increase until the tenth week of pregnancy (40), whereas blood lead was measured before week 10 for the majority of cases and controls (both means were approximately week 8, as shown in table 2).

If a long-term exposure affected women's capacity to carry to term, then use of whole blood lead rather than bone lead (which represents cumulative maternal exposure over decades) could have diluted the associations (41, 42). On the other hand, if the viability of a given pregnancy is more closely related to currently bioavailable lead, then blood lead would be preferable to bone lead. (Pregnancy-induced mobilization of bone stores would not have begun by the time the spontaneous abortions occurred (6).) In this case, plasma lead may be even more appropriate than whole blood lead (42, 43), but technical feasibility and cost were prohibitive for this study.

A potential source of confounding was the temporal variation in blood lead levels during the course of the study period (20). This problem was avoided by matching controls to cases on calendar time at enrollment. Neither life-style factors nor infectious diseases confounded the associations due to their low correlations with lead exposure and/or their low prevalence.

The use of self-report of spontaneous abortions could be a limitation in this study; however, given that these reports were made within a short time of the reported event and that the pregnancies had all been medically confirmed prior to the event, errors of recall seem unlikely. Overall, bias in the estimated associations due to under-ascertainment of recognized spontaneous abortions does not seem probable. Similarly, the possibility of false positives is unlikely, because we had laboratory confirmation of pregnancy for all women.

Although the quality of data may have differed between the private and public clinic patients as a result of differences in educational level and in the mode of administration of the questionnaires, these differences could not have introduced any bias, since cases and controls were matched on type of clinic and we conducted matched analyses. Because the women for this analysis were restricted to those who entered for prenatal care early in pregnancy, these women may have had better nutritional status than the general population of Mexico City. The shape and magnitude of the dose-response curve could therefore have been altered.

The possibility of selection bias due to differential loss to follow-up cannot be totally excluded. However, the mean blood lead level of women lost to follow-up was similar to that of the whole cohort and it fell between the mean of the cases and that of the controls. Furthermore, loss to follow-up was nondifferential with respect to clinic type, suggesting that differences between the 85 percent successfully followed and those lost to follow-up would have had a negligible effect on the findings. An additional potential source of selection bias is unrecognized early losses, not detectable unless pregnancy is diagnosed using close hormonal surveillance (44). The only scenario which could lead to artifactually higher lead in women with recognized spontaneous abortions would be if early unrecognized losses were *inversely* related to lead exposure. In other words, their blood lead levels would need to have been lower than the levels in surviving pregnancies (viz., a protective effect), on average. We have no data on unrecognized losses, but we know of no evidence supporting biologic plausibility of this scenario. On the contrary, animal studies suggest that lead can interfere with implantation or with sex steroid

production immediately following implantation (45–47), which would imply a possibly higher lead level in women who experienced early pregnancy losses. Thus, any association between lead and total pregnancy losses by week 20 might be stronger, not weaker, than the association we observed among the clinically recognized losses.

By a similar argument, if previous spontaneous abortions were associated with elevated blood lead levels in those earlier pregnancies, our analysis, which adjusted for previous loss, theoretically could have resulted in an underestimate of the true association with lead (48). However, removal of previous spontaneous abortions from the model had no impact on the coefficient or standard error for blood lead level.

Using a study design that avoids the pitfalls of many recent reports on this topic, we observed that increased blood lead level was associated with an elevated risk of spontaneous abortion among women in Mexico City. The risk rose in a dose-response manner, nearly doubling for each 5 μg/dL increase in blood lead. The mixed findings in recent studies of humans exposed environmentally (13–19) may have been a result of inadequate control for confounders in some instances, non-comparable timing for measurement of exposure among cases as compared with survivors, or differences in susceptibility among the various populations studied (e.g., nutritional status and other environmental exposures may modify the effect of lead (49, 50)).

The findings from this study provide evidence that lead may increase the risk of spontaneous abortion at currently encountered exposure levels, but further studies are needed to confirm these results. Such studies should also address the possibility of an artifactual association resulting from menstrual irregularity among women with higher lead levels.

The range of lead exposures in this study was 1.4 to 29 μg/dL, with a mean among controls of 10 μg/dL; these levels of exposure, although common in the US general population during the 1970s, are rare in the US general population today. They are, however, still common in many parts of the world, and are far lower than occupational exposures or the acceptable standards for these exposures in either Mexico or the United States. If our findings are confirmed, lead may be an important contributor to pregnancy loss in populations with similar or higher exposures.

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EXHIBIT 10

The Impact of Toxins on the Developing Brain

Bruce P. Lanphear[1,2]

[1]Child and Family Research Institute, BC Children's Hospital, University of British Columbia, Vancouver, British Columbia V5A 1S6, Canada

[2]Faculty of Health Sciences, Simon Fraser University, Vancouver, British Columbia V6H 3V4, Canada; email: blanphear@sfu.ca

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Keywords

environmental exposures, environmental toxins, behavioral problems, disabilities, ADHD, autism, mental disorder

Abstract

The impact of toxins on the developing brain is usually subtle for an individual child, but the damage can be substantial at the population level. Numerous challenges must be addressed to definitively test the impact of toxins on brain development in children: We must quantify exposure using a biologic marker or pollutant; account for an ever-expanding set of potential confounders; identify critical windows of vulnerability; and repeatedly examine the association of biologic markers of toxins with intellectual abilities, behaviors, and brain function in distinct cohorts. Despite these challenges, numerous toxins have been implicated in the development of intellectual deficits and mental disorders in children. Yet, too little has been done to protect children from these ubiquitous but insidious toxins. The objective of this review is to provide an overview on the population impact of toxins on the developing brain and describe implications for public health.

ENVIRONMENTAL DISASTERS

The impact of toxins on the developing brain was first recognized in the aftermath of environmental disasters (103). In the early 1900s, in an epidemic of lead poisoning from paint in Queensland, Australia, children presented with frank anemia, paralysis of the lower limbs, and blindness; many died (125). In the 1950s, in a Japanese fishing village on the shores of Minamata Bay, mothers who ingested mercury-contaminated fish gave birth to children with severe motor dysfunction and mental retardation (51). The epidemic of congenital mercury poisoning in Minamata—as well as the thalidomide-induced epidemic of phocomelia (seal-limb) in the 1950s—made it clear that, contrary to prevailing beliefs, the placenta is not a barrier against toxins (70). In 1955, in Japan, ingestion of arsenic-contaminated powdered milk by children resulted in more than 12,000 cases of arsenic poisoning. Children who had been exposed to arsenic-contaminated milk were 10 times more likely to be mentally retarded as compared with national rates (87). In 1968 in Japan and in 1979 in Taiwan, the ingestion of polychlorinated biphenyl (PCB)-contaminated rice bran oil by pregnant women led to fetal wasting and cola-colored, "dull" children (26, 103). These epidemics served as warnings that environmental toxins can adversely impact or retard brain development.

These disasters seem remote, but evidence has accumulated over the past century that implicates ubiquitous, low-level exposures to an ever-growing litany of environmental toxins in the development of diminished birth weight, shortened gestation, intellectual deficits, and mental disorders in children. The consequences of low-level exposures are usually subtle for an individual child, but the population impact on brain function can be substantial (10, 43, 47). Not surprisingly, the impact of environmental toxins on brain-based disorders is often overlooked, underestimated, or ignored.

NEW MORBIDITIES

The causes of death and disability in children have shifted over the past century. Concerted public health efforts to control tuberculosis, cholera, typhoid, and other infectious agents in the early twentieth century led to a dramatic reduction in child mortality, followed by a rise in life expectancy. By the end of the twentieth century, the "new morbidities of childhood"—attention deficit hyperactivity disorder (ADHD), autism, asthma, obesity, and preterm birth—had emerged. Learning disabilities and mental disorders are now two of the most prevalent morbidities in children. About 7.6% of US children are estimated to have a parent-reported learning disability, and 13% are estimated to have a mental disorder, including anxiety, autism, conduct disorder, depression, or ADHD (14, 20, 21, 44, 76) (**Figure 1**).

The prevalence of developmental disabilities has increased in US children. From 1997–1999 to 2006–2008, Boyle et al. (14) noted a 17% increase in the prevalence of parent-reported

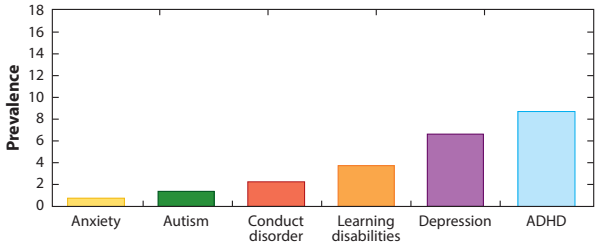


Figure 1

Prevalence of learning disabilities and mental disorders in US children. Data from 14, 21, 76.

developmental disabilities, representing an additional 1.8 million US children having a developmental disability. The prevalence of autism has increased dramatically, even after accounting for severity of symptoms, access, age at diagnosis, and immigration (53). The Centers for Disease Control and Prevention (CDC) (21) reported a 123% increase from 2002 to 2010 in the prevalence of autism spectrum disorder (ASD) among 8-year-old children, the age of peak prevalence, in a regional network. Using the National Survey of Children's Health, the CDC (20) also reported that the percent of children who had parent-reported ADHD increased by 22%, from 7.8% in 2003 to 9.5% in 2007. Quantifying trends in mental disorders is often limited by our reliance on parent-reported diagnosis and surveillance. Still, these data indicate that we are in the midst of an epidemic of brain-based disorders.

VULNERABILITY OF THE DEVELOPING BRAIN

The developing brain is particularly vulnerable to environmental toxins. The blood–brain barrier of the developing brain is not fully formed, and it is more permeable to toxins than is the mature brain (104). The rapid growth of the brain during the second trimester of fetal development is followed by neuronal migration, differentiation, proliferation, and pruning throughout early childhood (104). Growing cells are more vulnerable to toxins, and the brain forms over a longer period than do other organs (101, 104). Finally, the brain is composed of many different types of neurons, each type having a distinct growth phase and potentially a different toxicity profile (104).

Environmental toxins can impact the developing brain through various mechanisms. Some toxins, such as mercury, cause cell death and alter cell migration and cell proliferation (101, 104). Lead disrupts neurotransmission, synaptogenesis, and synaptic trimming (101, 104, 110). Dichlorodiphenyl trichloroethane (DDT), PCBs, polybrominated diphenyl ethers (PBDEs), phthalates, and bisphenol A appear to act—at least in part—by disrupting estrogenic or thyroid hormones (17, 28, 27, 74). Another potential mechanism by which toxins may impact brain development is through epigenomic alterations—heritable alterations in gene expression that do not entail changes in the DNA sequence (5). Many environmental toxins, including airborne pollutants, arsenic, lead, diethylstilbestrol (DES), tobacco, and bisphenol A, alter the methylation pattern of the epigenome, one of the more well-understood types of epigenetic modifications (5, 42, 90, 94). Still, epigenetic alterations have yet to be directly linked with neurobehavioral effects in children. Understanding the mechanism of toxicity is important, but it is not essential to regulate a chemical or pollutant.

During fetal development, the brain is particularly vulnerable to some toxins, such as methyl mercury and PCBs (39, 56, 61, 107–109). Methyl mercury affects proliferation and migration of neurons; methyl mercury and PCBs both affect synaptogenesis (101). These processes occur predominately during fetal development. In contrast, the brain is particularly vulnerable to lead exposure during early childhood (55, 110). Lead exposure interferes with synaptogenesis, the trimming of synaptic connections, and myelination; the latter two processes occur predominantly during childhood (101, 104). For most toxins, there is insufficient evidence to draw any firm conclusions about specific windows of vulnerability. For example, exposure to PBDEs has been studied in five prospective birth cohort studies (24, 36, 46, 52, 106), but only two tested whether prenatal or postnatal PBDE exposure was more strongly associated with neurobehavioral end points (36, 46). Eskenazi and her colleagues found that certain end points were more strongly associated with prenatal PBDE exposures, whereas other end points were more strongly associated with childhood exposures (36). Gascon and coworkers found that childhood but not prenatal exposures elevated attention deficit symptoms (46). Thus, although we know the developing brain is especially vulnerable to the impact of toxins, the specific windows of vulnerability are not well

characterized for many toxins. Moreover, different regions of the brain may have distinct windows of vulnerability for the same toxin.

Other factors can contribute to the heightened sensitivity of the developing brain to toxins. In some cases, such as with mercury, the concentrations in the fetus are higher than those found in the mother (96). The fetus or newborn may also lack critical enzymes to metabolize environmental toxicants, such as lower concentrations of PON1, an enzyme that has been shown to metabolize organophosphate pesticides (25). Young children are often more heavily exposed to toxins, such as lead, cotinine (a metabolite of nicotine and biomarker of tobacco exposure), and bisphenol A, than are older children and adults owing to differences in metabolism, mouthing behaviors, dietary intake, and respiratory rates (16, 66).

MEASURING EXPOSURE TO TOXINS

Biologic markers, or biomarkers, of exposure, which can enhance our ability to quantify an individual's internal dose of a contaminant, are revolutionizing the study of environmental toxins in the same way genetic tests are revolutionizing the study of heritability (65). Early studies of environmental toxins relied on questionnaires about diet, proximity to an industry, or age of housing to estimate exposure, but we can now use biomarkers to measure the internal dose of many environmental chemicals in human tissues and link these exposures with a disability or disease (112). Still, identifying the critical windows of vulnerability and determining how well a particular tissue reflects the target organ for a specific toxin can be challenging. Moreover, in the absence of innovative tools to measure biomarkers of exposure retrospectively (4), we will require large prospective birth cohorts to identify critical windows during fetal development for uncommon conditions such as autism.

The vast majority of people in the United States, including pregnant women and children, are routinely exposed to many confirmed or suspected toxins (134). The litany of toxins or suspected toxins that can be routinely detected in the blood or urine of pregnant women and children is extensive: metals (mercury, lead, cadmium, and arsenic), persistent pollutants (PBDEs, PCBs, and DDT), and nonpersistent chemicals (triclosan, pyrethroids, organophosphate insecticides, bisphenol A, and phthalates) to name only a few (134). Some of the contaminants are established neurotoxins or endocrine-disrupting chemicals, but most of them have not been tested for neurotoxicity (48). Nor has there been any systematic attempt to examine the impact of additive or synergistic effects of chemical mixtures.

Some critics have argued that the concentrations of environmental contaminants routinely found in pregnant women and children are too low to alter behavior. But, as described below, the concentrations of environmental contaminants shown to be toxic—that is, to alter brain function or behavior—are comparable with the therapeutic window for methylphenidate (5 to 30 ppb), the most commonly prescribed drug used to control or reduce ADHD symptoms in children (120).

THE IMPACT OF TOXINS ON COGNITION

Lead, PCBs, and mercury are established risk factors for cognitive deficits (49, 56, 61, 68, 82, 109, 113, 127). In a pooled analysis of 7 cohorts involving over 1,300 children, Lanphear and colleagues found that an increase in low-level, concurrent blood lead concentrations, from <1 to 10 μg/dL (<10 ppb to 100 ppb), was associated with a 6.9 IQ point decrement (68). Research on the relationship of prenatal exposure to PCBs—which consists of 209 related chemicals or congeners—is complicated by the degree of chlorination of the various congeners and types of tissue used to measure PCBs (113). Collectively, however, the epidemiologic and toxicologic evidence implicate prenatal PCB exposure in the development of intellectual deficits in children

(56, 114, 113, 127). In a systematic review, Karagas and coworkers found consistent evidence of adverse effects of prenatal mercury exposure on cognitive abilities in preschool children; the effects were less consistent for younger children and for studies that did not adjust for fish intake (61).

Other toxins have been consistently, but not definitively, associated with cognitive deficits in children. In three birth cohort studies, prenatal exposure to organophosphate pesticides was consistently associated with cognitive deficits in children (12, 35, 97). DiFranza and colleagues conducted a systematic review and concluded that prenatal tobacco exposure is likely associated with cognitive deficits in children, but the effects of exposure were attenuated with adjustment for other confounders (34). Airborne pollutants, using either polycyclic aromatic hydrocarbons or black soot as measures of exposure, have been linked with cognitive deficits in four prospectively followed birth cohorts (91–93, 115, 119). In one of these birth cohorts, the investigators showed an improvement in cognitive outcomes among children who were born after closure of a power plant (119). Five prospective birth cohort studies have examined the effects of exposure to PBDEs (24, 36, 46, 52, 106). PBDEs were inversely associated with cognition in four of the five studies; the results were statistically significant in three studies (24, 36, 52).

Still other toxins have been tentatively associated with cognitive deficits in children. Prenatal exposure to DDT has been associated with cognitive deficits in two of four prospective birth cohort studies (38, 37, 58, 77, 100, 123). Arsenic and manganese have been inversely associated with cognition in cross-sectional studies (75, 128, 129).

When does a suspected toxin become an established one? It is not entirely clear how much evidence is necessary to implicate an environmental contaminant or pollutant as a neurotoxin. In contrast with carcinogens, which are regularly and systematically evaluated by the International Agency for Cancer Research (IARC), there is no systematic process or criteria by which to evaluate emerging neurotoxins. This lack of formal procedure is unfortunate because it delays both the recognition of a toxin as well as any prevention efforts. Carcinogens have historically been singled out as being of paramount importance, but do toxins that impact the developing brain deserve any less attention?

QUANTIFYING THE IMPACT OF TOXINS ON BRAIN DEVELOPMENT

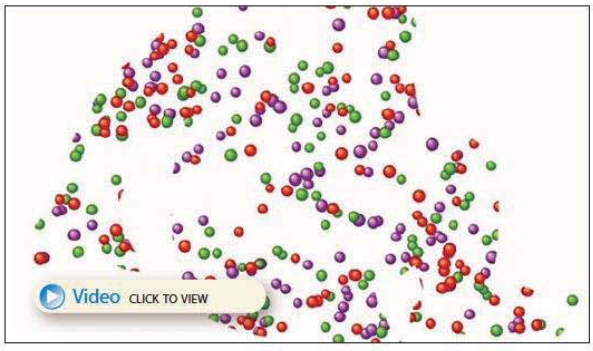
Quantifying the impacts of low-level toxin exposure on brain development is difficult. Many of these challenges result from our reliance on observational studies to investigate the effects of toxins in humans; it is notoriously difficult to infer causal associations from nonexperimental study designs. First, to quantify the independent contribution of a toxin, one must account for a variety of other factors that can impact brain development, including nutrition, maltreatment, and poverty (33). Second, there is substantial interindividual variability in the uptake and metabolism of toxins by a fetus or child owing to mouthing behaviors, genetic variability, and nutritional status. Third, toxins elevate the risk for prevalent but often nonspecific conditions or disorders, such as IQ deficits and ADHD, which makes it difficult to infer causality. Finally, it is difficult to distinguish the adverse effects of toxins from those of other social influences because impoverished children are often more heavily exposed to toxins than are affluent children. Given these obstacles—and a strict adherence to a high but arbitrary threshold for categorizing an association as statistically significant (81)—it is remarkable that the evidence linking numerous toxins with neurobehavioral insults is so robust and consistent. Still, because of the inherent challenges of observational studies, we often must rely on toxicologic studies to provide definitive evidence that environmental contaminants are toxic (69).

Once a toxin is identified, it is important to examine the shape of the dose–response relationship and ascertain whether the evidence supports a threshold. Toxins that impact brain development

are regulated as though there is a threshold, as though there is a safe level of exposure. For lead, the prototypical toxin, there is no evidence of a threshold; indeed, decrements in intellectual abilities are proportionately greater at the lowest levels (19, 68). Previous studies estimated that a 2–2.5 IQ point decrement has been linked with an increase in whole blood lead levels from 10 μg/dL (100 ppb) to 20 μg/dL (200 ppb) (68). In a pooled analysis, an increase in concurrent blood lead levels from <1 μg/dL (<10 ppb) to 10 μg/dL (100 ppb) was associated with a 6.9 IQ point deficit (68). Since then, more than a dozen articles have confirmed that blood lead concentrations are associated with IQ deficits or diminished academic abilities at levels <10 μg/dL (<100 ppb); when the investigators carefully examined the shape of the dose–response relationship, they confirmed that there were proportionately greater decrements at the lower levels of exposure (69, 80). In 2012, the CDC concluded that there is "no safe level of lead exposure"—a simple declaration with profound policy implications (22). Toxins have been regulated with the assumption that there is a threshold or a safe level of exposure. But what if there isn't one?

The shape of the dose–response relationship is not well established for many toxins. Yolton and coworkers found proportionately steeper decrements in reading abilities at the lowest levels of secondhand smoke exposure among US children, but this finding has not been replicated (137). For other established or emerging toxins, such as PCBs, organophosphate pesticides, and PBDEs, the lowest level at which adverse effects occur is less clear, but the linear relationship does not suggest a threshold (12, 24, 36, 52, 97, 113, 114). In contrast, some evidence supports a threshold for some mercury-induced deficits (108).

The impacts of toxins on the developing brain are often dismissed because the effects are subtle. Yet, subtle shifts in intellectual abilities or behaviors in a population can have a substantial impact on intellectual abilities (**Video 1**). It is not easy to discern a 5-point IQ difference between two children, but a 5-point downward shift in the population mean IQ, from 100 to 95 points, would result in a 57% increase in the number of children who have an IQ <70 points and a corresponding decrease in the number of children who have an IQ >130 points (**Figure 2**) (47). Bellinger calculated the population-wide impact of environmental toxins and other medical problems on IQ deficits in a contemporary six-year birth cohort of US children (10). The impacts of low-level exposures to lead, mercury, and organophosphate pesticides on decrements in IQ scores in US children were surprisingly large, even in comparison with clinical conditions, such as ADHD and preterm birth (10). See **Figure 3**.



Video 1

Subtle shifts in the intellectual abilities of individual children from widespread exposures to toxins can have a big impact on the number of children in a population who are intellectually challenged or gifted.

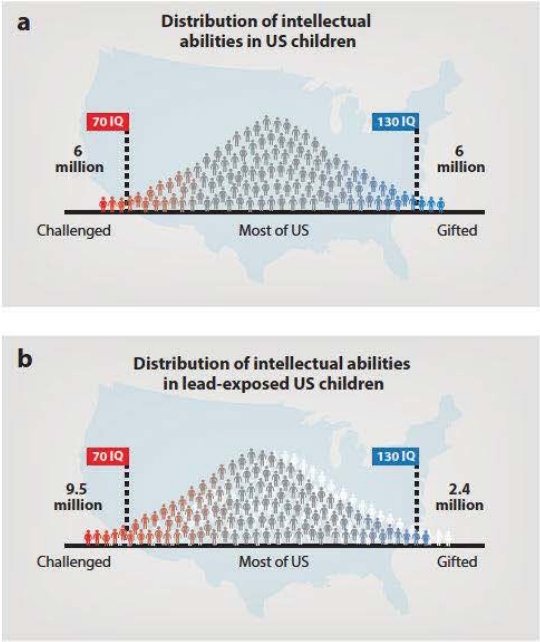


Figure 2

Little shifts matter. It is difficult to discern a 5-point IQ difference between two children, but a downward shift in the population mean IQ, from 100 to 95 points, results in a 57% increase in the number of children who have an IQ <70 points, from 6 million to 9.4 million, and a corresponding decrease in the number of children who have an IQ >130 points (panels *a* and *b*). Adapted from Reference 47.

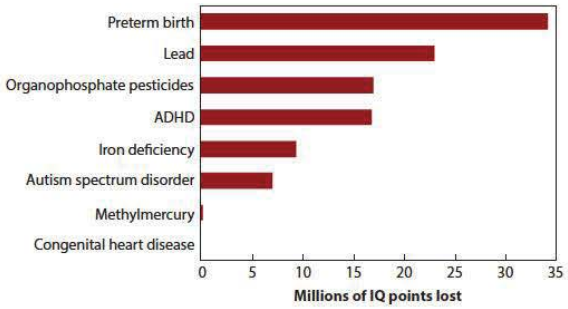


Figure 3

Estimated reduction in IQ points in a six-year cohort of US children for various risk factors. Adapted from Reference 10. Abbreviation: ADHD, attention deficit hyperactivity disorder.

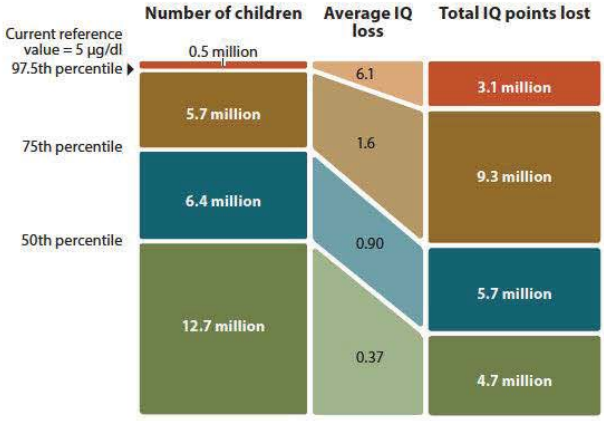


Figure 4

Prevention paradox. The majority of IQ points lost to lead exposure occur in children who have low-to-moderate exposure to lead. Adapted from Reference 10.

THE PREVENTION PARADOX

The cumulative impact of exposures to various subtle environmental influences or toxins that only modestly impact intellectual abilities can be substantial (130). Although the evidence for many of the emerging toxins—such as PBDEs, manganese, DDT, arsenic, and airborne pollutants—is not as conclusive as that for lead, PCBs, or mercury, the emerging evidence clearly shows that the cumulative impact of environmental toxins on children's intellectual abilities has been underestimated (79).

Once researchers identify a toxin, the typical strategy is to target high-risk children. This strategy, which is based on the medical model, is efficient; children who are at high risk typically exhibit more severe or overt effects than do less-exposed children. Still, unless a threshold exists, the high-risk approach will inevitably fail to protect the majority of individuals who experience deficits. The failure of the high-risk approach to protect most cases—cases that occur in low-to-moderate risk groups—is called the prevention paradox (105).

Lead-associated IQ deficits offer a compelling example of the prevention paradox. The CDC recently concluded that there is no safe level of lead exposure in children but, owing to inadequate resources, recommended using a reference value of 5 µg/dL (50 ppb) (representing the 97.5th percentile for blood lead levels in US children) for case management (22). Targeting children who have a blood lead concentration >5 µg/dL (50 ppb) is efficient; the average lead-associated IQ loss for these children is considerably larger (or greater) (6.1 IQ points) than is the loss in those who have lower blood lead concentrations (**Figure 4**). Yet children who have a blood lead concentration >5 µg/dL account for fewer than 3 million (~18%) of the 23 million IQ points lost due to lead toxicity. Thus, by focusing on high-risk children, we will ultimately fail to protect the majority of children who are adversely affected by lead and other toxins.

Toxins can have a lifelong impact on brain function (83, 132, 135). Children who have higher blood lead concentrations may never meet the same peak cognitive ability in adulthood as that in less exposed children (**Figure 5**). At the other end of the age spectrum, cognitive decline is accelerated in adults who have higher bone lead concentrations (111, 131). If this trajectory

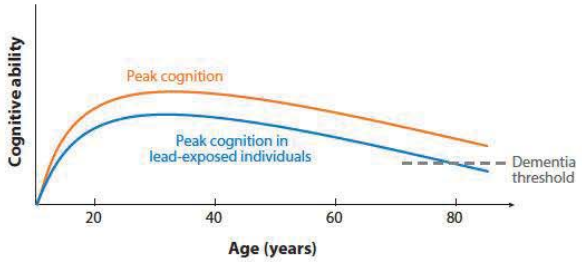


Figure 5

Lifetime impact of low-level lead exposure on cognitive function.

continues, lead-exposed adults would reach the diagnostic threshold for dementia sooner than those who have lower bone lead concentrations. Indeed, some evidence has shown that early-life lead exposure is a risk factor for the development of late-onset Alzheimer's disease (6, 7, 136). With the exception of those for lead, few birth cohorts have been studied into adulthood; however, it would be surprising if the effects of other toxins observed in school-aged children do not persist into adulthood.

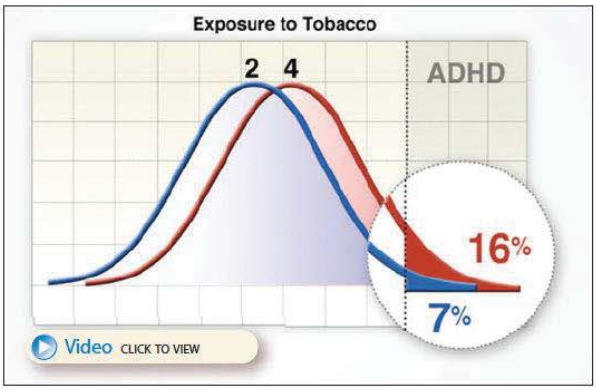
ADHD

ADHD, the most common brain disorder of childhood, affects about 1 in 10 children in the United States; boys are 2.5 times more likely to meet criteria for ADHD than are girls (44). ADHD is not a specific disorder, but a medley of maladaptive deficits and behaviors, the most prominent of which are hyperactivity, impulsivity, and inattention (3, 65). Children who have ADHD often have other comorbid conditions; about one in two children who have ADHD also have a learning disorder (3).

Exposures to some environmental toxins—especially lead and tobacco—are recognized risk factors for ADHD (39, 43, 59, 64, 65, 80, 86). Using brain imaging, researchers have shown that childhood lead exposure as well as prenatal exposures to tobacco and organophosphate pesticides are associated with alterations in brain structure that are consistent with ADHD (18, 23, 72, 98, 117). The data are sparser for other toxins, but a flurry of new studies suggests that organophosphate pesticides, mercury, PBDEs, PCBs, perfluorinated compounds (PFCs), phthalates, bisphenol A, and airborne pollutants may be risk factors for ADHD or ADHD-related behaviors (11, 13, 16, 36, 54, 62, 85, 92, 93, 97, 107, 108). Many toxins, such as lead, PCBs, bisphenol A, manganese, and mercury, disrupt dopamine or dopaminergic neurons in the prefrontal cortex (1, 57, 110). This disruption is consistent with the hypothesis that ADHD is due to a deficiency or imbalance of dopamine in the prefrontal cortex (117).

It should not be surprising that various toxins can increase the risk for ADHD; ADHD is a syndrome of behaviors and deficits that exist on a continuum (65). Environmental lead exposure increases certain ADHD-related behaviors, such as impulsivity, attention, and aggression (29, 39, 73, 82, 122). Bisphenol A exposure has been associated with anxiety and hyperactivity (16, 89). Exposure to various toxins—each of which may increase the frequency of one or more ADHD-related behaviors or deficits by a modest amount—can result in a substantial increase in the overall prevalence of ADHD.

Using National Health and Nutrition Examination Survey (NHANES) data, we found that, among 8- to 15-year-old US children, those who had blood lead concentrations in the lowest tertile (<0.7 μg/dL) (<7 ppb) exhibited, on average, only one ADHD symptom, whereas children in the highest tertile of blood lead levels (>1.3 μg/dL) (>13 ppb) exhibited three symptoms (43). This



Video 2

Using a nationally representative study of US children, this video illustrates how subtle shifts in ADHD symptoms from childhood lead exposure and prenatal tobacco exposure result in a large increase in the percent of US children who have ADHD.

subtle shift in the population distribution of ADHD symptoms led to a twofold increase in the percent of children who met criteria for ADHD, from 5% to 13% (**Video 2**). Similarly, children who were unexposed to tobacco during fetal development exhibited two ADHD symptoms, whereas tobacco-exposed children exhibited four symptoms. The subtle shift in symptoms led to a twofold increase in the percent of children who met criteria for ADHD, from 7% to 16%. Children who were exposed to high childhood blood lead concentrations and prenatal tobacco smoke were eight times more likely to meet criteria for ADHD than were children who had neither exposure. We estimated that about one in three cases of ADHD in US children—equivalent to about 1 million children—is attributable to childhood lead exposure and/or prenatal tobacco exposure.

AUTISM

Autism, or ASD, is a brain-based disorder characterized by impaired social communication and repetitive or stereotypic behaviors with onset before three years of age (3). The prevalence of autism in the United States is estimated to be ~1 in 68 children, but it is higher in males (21). Until recently, the search for potential environmental factors in the development of autism was overshadowed by the search for genetic factors. It is now increasingly recognized, if not fully acknowledged, that environmental factors play an equally important role in the development of autism (50, 118).

A few environmental risk factors for autism have been tentatively identified, including folate status (45, 95, 116), environmental chemicals or drugs (17, 31, 63), and airborne pollutants (8, 60, 102, 126, 133). Folate status appears to be a key risk factor for autism and ASD. Folate supplementation has been associated with a lower risk for the development of autism (116). Folate receptor blocking antibody is significantly higher among parents of autistic children than among parents of nonautistic children (45, 95). Valproic acid, an inhibitor of folate, is also a risk factor for the development of autism (31). It is not clear whether folate is a modifier or an independent risk factor for autism, but its role in the development of autism deserves closer scrutiny.

Five studies have examined the association of airborne pollutants, including metals, diesel, and particles <2.5 microns in diameter ($PM_{2.5}$), with autism or ASD (8, 60, 102, 126, 133). Although all

these studies found significant associations with one or more components of airborne pollutants, they did not consistently identify the same pollutant. Perhaps this result is to be expected; autism, like ADHD, is a medley of maladaptive behaviors and deficits, each of which might be affected by one or more toxins. Still, replication is essential for determining whether specific components of air pollution are risk factors for autism or ASD.

These studies only cast a dim light on various potential risk factors for the development of ASD, but they are beginning to identify clues to the autism epidemic. Studies that can measure exposures that occur during critical developmental windows, especially during early pregnancy, are critical for exploring risk factors for autism and ASD.

ANTISOCIAL BEHAVIORS

Can ubiquitous exposure to a toxin result in widespread social dysfunction? (73). Lead exposure is a potent predictor of behaviors linked with delinquency and criminality, such as impulsivity, hyperactivity, and aggressive behaviors (29, 41, 73, 122). In experiments with rodents and nonhuman primates, early lead exposure caused abnormal mother–infant interactions, higher rates of antagonistic interactions, and reduced social play (32, 71). In a meta-analysis of 16 studies, Marcus concluded that lead exposure, measured using blood lead or bone lead concentrations, was a risk factor for conduct disorder (73). In a nationally representative sample, Braun and colleagues found that 8- to 15-year-old children who had blood lead concentrations in the highest quintile (>1.5 μg/dL) were 8 times more likely to meet diagnostic criteria for conduct disorder than were those in the lowest quintile (15). Only two prospective birth cohort studies have examined the impact of childhood lead exposure on antisocial behaviors; both reported that lead was a risk factor for higher rates of criminal arrest in young adults (40, 135). In two separate analyses, Nevin (84) and Reyes (99) both concluded that the downward trend in crime, especially violent crime, was due largely to the decline in blood lead concentrations. Collectively, these studies provide compelling evidence that childhood lead exposure played a central role in the epidemic of violent crime over the past century and illustrates how widespread exposure to a prevalent toxin can alter the social landscape.

THE COST OF TOXINS

The cost of toxins that impact brain development is substantial. Trasande & Liu estimated that the cost of exposures to lead, mercury, and other toxins that affect intellectual abilities exceeds $70 billion annually in the United States (124). This figure is obviously an underestimate because it does not account for the effects of other suspected toxins, such as organophosphate pesticides, PBDEs, or air pollutants. Moreover, it does not account for the cost of research to explicate the toxicity of environmental chemicals or to clean up contaminated communities. Finally, and perhaps most important, it does not account for the cost of human suffering: the impact these toxins have on children's ability to function in their daily lives and the accommodations that parents and society must make for them.

LIMITATIONS AND CONFOUNDING

Observational studies that are designed to investigate the impacts of toxins on the developing brain are limited in their ability to infer causal associations (69). First, because the exposures are not randomly assigned, there will always be a potential for unmeasured confounding. Second, some studies failed to collect or adjust for potentially important confounders, such as nurturing behaviors in the home environment (e.g., the HOME Inventory) or breastfeeding (33). Other studies did not account for exposure to secondhand smoke or other environmental toxicants or for

iron status. Most studies did not account for parental psychopathology. Indeed, there is an endless litany of potential confounders to consider, a limitation of observational studies that is often used to thwart efforts to regulate environmental toxins despite compelling evidence from both human and laboratory studies (69).

We usually worry about unmeasured confounders that may erroneously inflate the estimated association of a toxin with a deficit or disorder, but confounders can also diminish a true association (9, 30, 65). Low-level mercury exposure in fish-eating populations has been linked with deficits in cognition in some studies but not others (49, 61, 78). Ultimately, some of the conflicting results were shown to result from confounding; the beneficial effects of fish intake repressed the toxic effects of mercury exposure (30, 88). This result raises important questions about how the effects of other suspected toxicants, such as organophosphate pesticides, which are higher in pregnant women and children who ingest large quantities of fruits and vegetables, may be difficult to disentangle from beneficial nutrients.

Despite these limitations, the pattern of toxicity that has emerged over the past century is clear; low-level exposure to insidious toxins during critical windows of brain development can have lifelong impacts on an individual's ability to function and on social dysfunction. The impacts are more profound at the population level. It is not clear why more has not been done to protect children from toxins that impact brain development, but clearly we urgently need to expand our focus on prevention.

PREVENTION

The optimal strategy to prevent the development of brain-based disorders is to identify and restrict or ban the use of potential toxins before they are marketed or discharged into the environment. Unfortunately, industries are allowed to market a product until it is repeatedly shown to be toxic in both human and laboratory studies. Once a toxin is disseminated in the environment, it requires a Herculean effort to disentangle its effects from other prevalent and modifiable risk factors for brain-based disorders. There are likely to be many risk factors because brain-based disorders represent an array of behaviors or deficits that exist on a continuum. This fact should be obvious, but it is surprising how frequently we pit one risk factor against another in our ongoing search for the ever-elusive cause of disabilities in children.

Intellectual deficits or brain-based disorders in children are still often thought to result predominately from poor parenting or genes; it is not unusual, for example, to read that genes account for 70% of autism or ADHD (118, 121). But it is now widely accepted that most complex diseases and disorders, including ADHD and autism, are due to the interplay of genes and environment. Thus both genetic and environmental risk factors are necessary for most cases of brain-based disorders to develop.

Despite considerable evidence implicating toxins in the development of intellectual deficits and mental disorders in children, our efforts to control or eliminate exposure to toxins have been inadequate. Most of the contaminants and toxins readily found in human tissues—such as lead, flame retardants, bisphenol A, and phthalates—did not undergo premarket testing (70). Instead, we haphazardly conduct studies after pregnant women and children are routinely exposed to toxins or suspected toxins to untangle the toxic effects of a particular contaminant from a multitude of other risk factors.

Our initial efforts to prevent exposures to toxins typically focus on education. We pass out pamphlets, advise parents to wash their child's hands and to avoid fish that is heavily contaminated with mercury or PCBs, and admonish them not to smoke tobacco products around children or pregnant women. Education offers some small, short-term benefits, but we will inevitably fail

to protect children until we reduce or eliminate the source of toxins. The dramatic reduction in childhood lead poisoning had little or nothing to do with passing out mop buckets or admonishing mothers to wash their child's hands; blood lead concentrations plummeted because lead was phased out of gasoline and banned for use in paints, solder, and other consumer products (67). There is some potential benefit when companies, such as Walmart, phase out products that contain phthalates or other suspected toxins owing to consumer pressure, but these voluntary actions will inevitably fail to protect children because of the large number of chemicals in the marketplace and the tendency to replace confirmed or suspected toxins with other, largely untested chemicals. The only comprehensive preventive strategy is to revise the regulatory framework for environmental chemicals and industrial pollutants and ensure they are not toxic before they are marketed or discharged into the environment (2, 70).

How much evidence is necessary to ban, control, or restrict the use of a suspected or confirmed toxin? Using the principle, "first, do no harm," we have appropriately required evidence from randomized controlled trials before health care providers prescribe a drug. In contrast, we have placed the burden on parents, scientists, pediatricians, and policy makers to prove that suspected toxins are hazardous after they have been used in consumer products or widely disseminated in the environment. There is now sufficient evidence to shift the burden of proof and require industry to prove that the chemicals used in consumer products and the pollutants emitted from their plants are not toxic.

Several steps are necessary to protect children from toxins that impact the developing brain. First, we need to revise the regulatory framework to require industries to provide evidence that chemicals used in consumer products are not toxic before products are marketed (2, 70). Second, we need to enhance the US Environmental Protection Agency's ability to set standards to evaluate the impact of environmental chemicals, industrial pollutants, and airborne toxics on the developing brain. Third, we need to devise and fund a national surveillance system to quantify the prevalence of and trends in learning problems and mental disorders. One way to enhance surveillance is to augment the NHANES (76) and the National Health Interview Survey (14) with validated instruments conducted at regular intervals to measure the prevalence of learning disabilities and mental disorders. Fourth, we need to establish independent, scientific panels to systematically evaluate the evidence linking toxins or suspected toxins with brain-based disorders and intellectual deficits. These panels, like those established for suspected carcinogens, would provide a scientific forum to draw conclusions about the evidence implicating particular toxins or types of toxins that affect brain development. The panels should also be mandated to recommend standards that provide a margin of safety. Finally, we need to convene a national task force to develop a strategy to prevent the development of intellectual deficits and mental disorders in children that encompasses all aspects of brain development, including universal access to early childhood education and the elimination of exposures to toxins.

Over the past 50 years, it has become clear that low-level exposures to environmental toxins can result in substantial disease and disability. Emerging evidence indicates that other ubiquitous chemicals are toxic. We can no longer deny the substantial if insidious impact that environmental toxins have on the developing brain. It is time to develop a comprehensive strategy to protect children from the impact of environmental toxins on the developing brain.

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65 case on behalf of the California Attorney General's Office, and a Canadian tribunal on trade dispute about using lead-free galvanized wire in stucco lathing, but he received no personal compensation for these services. Dr. Lanphear has served as a paid consultant on a US Environmental Protection Agency research study related to childhood lead poisoning and the California Department of Toxic Substances Control. Dr. Lanphear has received federal research awards from the National Institute of Environmental Health, the US Environmental Protection Agency, the Centers for Disease Control, and the US Department of Housing and Urban Development. He is also the recipient of federal research awards from the Canadian Institutes for Health Research and Health Canada.

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EXHIBIT 11

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Lead (Pb) in Tap Water and in Blood: Implications for Lead Exposure in the United States

SIMONI TRIANTAFYLLIDOU and MARC EDWARDS
Department of Civil and Environmental Engineering, Virginia Tech, Durham 418, Blacksburg, VA, USA

Lead is widely recognized as one of the most pervasive environmental health threats in the United States, and there is increased concern over adverse health impacts at levels of exposure once considered safe. Lead contamination of tap water was once a major cause of lead exposure in the United States and, as other sources have been addressed, the relative contribution of lead in water to lead in blood is expected to become increasingly important. Moreover, prior research suggests that lead in water may be more important as a source than is presently believed. The authors describe sources of lead in tap water, chemical forms of the lead, and relevant U.S. regulations/guidelines, while considering their implications for human exposure. Research that examined associations between water lead levels and blood lead levels is critically reviewed, and some of the challenges in making such associations, even if lead in water is the dominant source of lead in blood, are highlighted. Better protecting populations at risk from this and from other lead sources is necessary, if the United States is to achieve its goal of eliminating elevated blood lead levels in children by 2020.

KEY WORDS: blood lead level, correlation, health effects, dissolved lead, particulate lead, plumbing, regulations, tap water

I. INTRODUCTION

Lead (Pb) is widely recognized as one of the most pervasive environmental health threats in the United States. Dramatic progress has been made over

Address correspondence to Marc Edwards, Department of Civil and Environmental Engineering, Virginia Tech, Durham 418, Blacksburg, VA 24061, USA. E-mail: edwardsm@vt.edu

the last four decades to reduce lead exposure from gasoline, paint, dust, food/drink cans, and drinking water (Shannon, 1996). However, despite reduced exposure from nearly all sources, clinical evidence has demonstrated adverse health impacts at blood lead levels once considered safe (Fadrowski et al., 2010; Jusko et al., 2008). As a result, while the incidence of elevated blood lead (EBL) has markedly decreased, public sensitivity and medical concern about even low-level lead exposure has increased. In order for the United States to achieve its goal of eliminating all instances of EBL in children by 2020 (U.S. Department of Health and Human Services, 2010), improved understanding of exposure to all lead sources is necessary.

Defining a typical case for childhood lead exposure can be misleading, because lead exposure affects individuals whose behavior and environments are infinitely variable. Nonetheless, it is often stated that in the typical case, drinking water consumption is believed to account for up to 20% of total lead exposure nationally (U.S. Environmental Protection Agency [US EPA], 1993). But the US EPA also acknowledged that for infants consuming formula it may account for more than 50% of their total lead exposure, and further predicted that the relative importance of lead in water as a source would increase as other lead sources were being addressed (US EPA, 1991). Recent work has demonstrated that in some cases, lead from water can be the dominant source of exposure in children with EBL. For example, isolated cases of childhood lead poisoning in North Carolina and in Maine were tied to drinking water (Triantafyllidou et al., 2007). In addition, a 2009 study linked a period of very high lead-in-water contamination in Washington, DC, with increased incidence of EBL for the youngest children tested (Edwards et al., 2009). Finally, the Centers for Disease Control and Prevention (CDC) publicized preliminary results of an epidemiological study, which demonstrated associations between children's EBL and partially replaced lead water pipes (Frumkin, 2010).

The goal of this work is to conduct a critical review of the literature, with emphasis on the following:

- The release of hazardous levels of lead in tap water from old lead-bearing plumbing materials;
- Lead contamination of tap water as a public health concern even in modern buildings, and in cities that might meet federal regulations for lead in tap water;
- The absence of federal regulations for lead in drinking water of U.S. schools and day care facilities;
- The difference between dissolved and particulate lead release into tap water, and the challenges in monitoring and exposure assessment associated with the particulate lead fraction;

- Some of the challenges in associating water lead levels (WLLs) to blood lead levels (BLLs) in population studies or in case studies;
- Important aspects of population studies that did, or did not, find associations between lead in water and lead in blood.

II. SOURCES AND POTENTIAL IMPORTANCE OF LEAD IN TAP WATER

Sources of Lead in Tap Water

Drinking water usually contains little or no lead when it leaves the water treatment plant and as it travels through water mains (Figure 1). But as it enters building plumbing through service line connections, it may come into contact with lead-containing plumbing materials (Figure 1). These materials include lead pipe, lead-containing solder used to join copper and other metallic pipes together, and plumbing devices made of lead-containing brass (e.g., water meters, valves, components in water fountains and in faucets; Figure 1). As water flows through or sits stagnant in the pipes and in other plumbing devices, it can become contaminated with lead through a variety of complex electrochemical, geochemical, and hydraulic mechanisms (Schock et al., 1996). Lead that is released from the plumbing can contaminate water at the tap in one of two forms: as particulate lead or as dissolved lead (Figure 1). Ingestion of lead-contaminated water is a direct pathway to lead exposure (bathing and showering with that water are not expected to cause health problems because human skin does not absorb lead in water; CDC, 2010a).

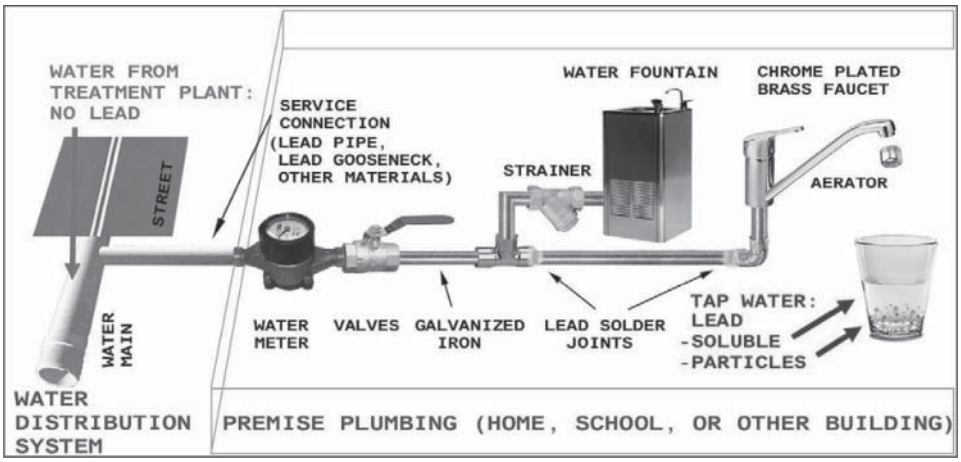

FIGURE 1. Potential sources of lead contamination in tap water of homes, schools, and other buildings.

Lead Pipe

Lead pipe was used for the conveyance of drinking water, because it is easily formed, cut, and jointed, and because its flexibility provides resistance to subsidence and frost (Schock et al., 1996). An advertisement by the National Lead Company in 1923 (Anonymous, 1923) illustrated that in many cities the law required that lead pipe alone be used to bring water from street mains into the building. Use of lead pipe in service lines was standard practice in many U.S. cities through the 1950s, and despite well-known health concerns was even occasional practice until the Congressional ban effective 1986. Considering health impacts from drinking water contamination, one historian characterized use of lead pipes in major cities as one of the most serious environmental disasters in U.S. history (Troesken, 2006). Even though the use of lead pipe in service lines or premise plumbing was prohibited in the United States by the Safe Drinking Water Act (SDWA) amendment of 1986 (US EPA, 2006a), older buildings may still be connected to lead service lines, lead goosenecks, and other pure lead components. Depending on their length and diameter, water corrosivity, water use patterns and hydraulic patterns, lead service lines generally account for 50–75% of lead contamination at the tap in older homes where they are present (Sandvig et al., 2008).

Partially Replaced Lead Pipe

In the United States, ownership of the lead pipe in service lines is typically shared between water utilities and homeowners. The controversial and expensive practice of replacing the utility's portion of an old lead service line with copper, while leaving behind the customer's portion, has been conducted in many cities with the purported goal of reducing lead in drinking water at the tap. Such replacements are termed *partial lead pipe replacements*. This practice can actually increase water lead concentrations at least in the short term (days to weeks), and for an undetermined duration beyond that time (Sandvig et al., 2008). The short-term effect is due to disturbance of the lead rust (i.e., corrosion scale) that has accumulated on the lead pipe over decades/centuries of use, or from creation of metallic lead particles when the lead pipe is cut. Recent research has also shown that in some situations, the creation of a galvanic cell (i.e., battery) between the lead pipe and the copper pipe may create serious water lead contamination in both the short term and longer term (Triantafyllidou et al., 2009a), confirming long-held concerns (Chambers and Hitchmough, 1992). This might explain the higher incidence of EBL in children living in homes with partially replaced lead pipe, when compared with homes with full lead pipes (Frumkin, 2010).

Lead Solder

Solder is a fusible metal alloy that is melted to join metallic plumbing materials together in a strong and water-tight seal (Figure 1). An increased lead content in the alloy improves ease of use and reduces leaks, and solder containing 40–50% lead by weight was used in U.S. buildings until banned in 1986. Thereafter, only lead-free solder, containing less than 0.2% lead by weight, was allowed in buildings. Lead solder is still available in hardware stores because it is legal for use in hobby electronics, and plumbers still illegally use lead solder in some new buildings in the United States (Goss, 2008) and in Scotland (Ramsay, 2003). In fact, a Scottish study found links between illegal use of leaded solder in new homes and blood lead of residents (Ramsay, 2003). The contribution of lead solder to lead in water at a given tap is extremely variable, and is dependent on the number of joints, their age, workmanship when the joint was created, surface area of the solder exposed to water at each joint, and the water chemistry (Sandvig et al., 2008). Recent cases of childhood lead poisoning from drinking water in North Carolina and in Maine were tied to lead solder particles that corroded and detached into the water supply (Triantafyllidou et al., 2007).

Brass (and Bronze) Plumbing Components

Brass and bronze are copper alloys that contain lead. Historically, lead was added to these alloys to reduce leaks (Showman, 1994). According to congressional definition, lead-free brass components (e.g., strainers, check valves, water meters, couplings, fittings, faucets, drinking fountains, bubblers, water coolers) used in modern homes can legally contain up to 8% lead by weight (Figure 1). The contribution of a brass component (e.g., a faucet) to lead levels measured at the tap depends on the lead content of the brass (typically ranging from 1.5 to 8% by weight), the volume of water in contact with the faucet, the physical configuration of the faucet and how it was manufactured, and the water corrosivity and water flow conditions (Sandvig et al., 2008).

Recent problems with persistent lead contamination of tap water (up to 300 μg/L lead) in new buildings at the University of North Carolina at Chapel Hill were attributed to lead-free brass/bronze ball valves, installed before drinking water fountains. Locating and removing these ball valves was necessary to eliminate the lead problems at the fountains (Elfland et al., 2010). There are also case studies in which elevated lead in water from brass was suspected to be the primary contributor to cases of childhood lead poisoning (CDC, 1994). Sampling of homes in the Netherlands also revealed some severe cases of high lead release (up to 5030 μg/L) from brass faucets (Slaats et al., 2007). New brass alloys have been developed that contain very low lead (0.1–0.25% lead by weight; Sandvig et al., 2008), and

California and several other U.S. states are beginning to require their use in new construction (Sandvig et al., 2008).

Other Lead Sources in Tap Water

Galvanized pipes are steel pipes coated with a protective layer of zinc, and high levels of lead can be present as impurities in the zinc coating (Schock et al., 1996). The iron rust in these pipes can also accumulate and store lead from other plumbing sources (HDR Engineering, 2009). Thus, even after lead pipe is replaced, lead accumulated in this iron rust can contribute elevated lead to tap water for years (HDR Engineering, 2009).

Rough Estimation of U.S. Households at Potential Risk

While poor record keeping makes it practically impossible to determine the exact type of plumbing materials at individual U.S. households, without exhuming and forensically evaluating plumbing materials underground and in walls, consideration of rough estimates is useful. Weston and Economic and Engineering Services (1990) determined through anonymous surveys of water utilities that there were about 3.3 million lead service lines and 6.4 million lead pipe gooseneck connections in the United States, corresponding to about 3% and 6% of total U.S. housing units, respectively (Table 1). For solder, it is estimated that the 81 million U.S. housing units (77% of total U.S. housing units) constructed prior to the federal ban of lead pipe and lead solder in 1986 (U.S. Census Bureau, 2000) are virtually certain to contain lead solder joints (Table 1). In addition, all housing units built after 1986 are almost certain to have lead-free brass plumbing devices that contain 1.5–8% lead by weight (Table 1). Only new housing units that incorporate nonleaded brass faucets and other nonleaded brass components (<0.1% lead by weight), can completely eliminate the presence of lead in plumbing, and it was only recently that such products could be purchased in nonleaded forms. It should be noted that the rough estimates presented (Table 1) refer to potential risk, and that like lead paint, degradation of leaded plumbing via corrosion and flaking of scale or rust to the water can dramatically increase the hazard to residents. In some situations lead in water for homes containing lead pipe, lead solder, or leaded brass is virtually below detection, due to formation of protective surface coatings.

To offer an additional perspective, simple calculations suggest that the mass of lead present in a typical lead service line is about 19 kg (Table 1). If only 0.1% of this lead pipe is eaten away at the pipe wall due to corrosion and is released to the water, the released lead mass of 19 g is sufficient to contaminate every drop of water used by a U.S. family of three for three years over the federal action level of 15 μg/L (calculation based on 1135 L/day water usage for the whole family). Before half the pipe wall (i.e., 50% of the lead pipe) is eaten away, likely subjecting the lead pipe to leaks and

TABLE 1. Estimated number of U.S. homes at potential risk from tap water lead contamination, depending on presence of lead-bearing plumbing materials

Lead-bearing plumbing material	Age of U.S. homes at potential Risk	Estimated number of US homes at potential risk (% of total)	Estimated mass of lead per home at potential risk (kg)
Brass plumbing components			
If 2% lead by weight	All	All	0.1[b]
If 8% lead by weight	All	All	0.3[b]
>8% lead by weight	Pre-1986	81 million (77%)[a]	0.4[b]
Lead pipes, lead service lines, and lead goosenecks (100% lead by weight)	Pre-1986	3.3–6.4 million[c] (3–6%)[a]	19.1[d]
Lead solder (40–50% lead by weight)	Pre-1986	81 million (77%)[a]	Highly variable, but believed to be very significant[e]
Lead joints in water mains (100% lead by weight)	Pre-1986	All homes served by water mains installed pre-1986	Unknown but believed inconsequential[f]

Note. The year 1986 marked the federal ban of lead pipe and lead solder, and established a maximum lead content of 8% by weight for lead-free brass plumbing components.

[a]Estimation based on year of home built from U.S. Census Bureau (2000). [b]Assumed one residential brass water meter of body weight 5 lbs (2.3 kg) and eight brass devices similar to brass ball valves of individual body weight 0.5 lbs (0.2 kg). [c]Estimation by Weston and Economic and Engineering Services (1990). More recent estimations have not been conducted. [d]Calculation for typical lead service line of 25 ft (7.6 m) length, internal diameter of $\frac{3}{4}$ inch, external diameter of 1 inch, and lead density of 11.3 g/cm^3. [e]Depends on workmanship of the soldering process at joints and resulting mass of solder in contact with water, believed one of the major sources of tap water lead contamination. [f]Currently believed that lead in these lead joints will not contact the water.

mandatory replacement with unleaded materials, the potential lead release is sufficient to contaminate every drop of water used by a family for 1,500 years. Coupled with the direct path to possible human ingestion, this analysis puts the potential magnitude of the lead pipe problem into perspective, and highlights the importance of corrosion control and safe water use practices in avoiding potentially harmful exposure. In 1993, the US EPA estimated that more than 40 million U.S. residents used water that can contain lead in excess of the federal action level of 15 μg/L (US EPA, 1993).

Lead pipes are more common in other countries. For example, the percentage of lead service lines in France, the United Kingdom, and Germany as of 1999 was estimated at 40–50% (Hayes and Skubala, 2009). As of 1999, premise (building) plumbing in Portugal, France, and the United Kingdom also contained 30–40% lead pipes (Hayes and Skubala, 2009). In Japan, as of 2002, a total of 667 km lead pipe was found below roads and 3,248 km of lead pipe was found in residential areas (Osawa, 2002).

Other Sources of Environmental Lead Exposure and Perceptions Regarding Their Relative Importance

Lead products have been used in numerous other applications, all of which constitute potentially harmful exposure sources worthy of mitigation. Before improvements in corrosion control reduced lead in potable water in the 1950s and then again in the 1970s (Karalekas et al., 1976; Moore et al., 1985), it was widely accepted that lead in water was a dominant pathway of human exposure and that high incidence of miscarriages and in infant and even adult mortality were attributable to this source (Renner, 2007; Troesken, 2008, 2006;). While it is accepted that exposure to lead from any source is potentially harmful, maximizing public health gains with scarce available financial resources has necessitated creation of a modern hierarchy of perceived risk and reward for public health interventions. This, in turn, has occasionally put the different lead sources in competition with one another.

Some individuals in the lead poisoning prevention community have expressed a fear that focus on lead in drinking water reduces attention on other, and potentially more important, sources of lead in the household environment (e.g., paint, dust; Blette, 2008). This mindset reinforces reports that in the early 1990s the then CDC director of the former Center for Environmental Health railed against doing much in drinking water because he did not want to disarm lead in paint (Powell, 1999). There has been some speculation that the scientific presentation of research results and public health messaging, in response to a well-publicized incident of elevated high lead in drinking water of Washington, DC, was affected by these concerns (Edwards, 2010; Miller, 2010). On occasion, the lead paint water risk reward analysis has

been invoked to justify diverting a portion of funding originally intended for reducing the public's exposure to lead in water, toward the creation of lead paint educational programs (Renner, 2010). It is important to acknowledge these issues, because neither scientists nor popular belief can be assumed to be completely immune from preconceptions, and continued debate about where to invest scarce resources will intensify with reduced availability of funding.

Clearly, peeling lead paint chips and associated dust pose a great health concern to U.S. children (Jacobs 1995; Levin et al., 2008). Although the conventional wisdom in the United States is that lead-based paint is the predominant source of lead poisoning in children, and all other lead sources are a distant second, a few potential weaknesses in this argument and alternative perspectives have been provided by authors such as Mielke and Reagan (1998). Based on their work, lead in soil and in dust, even when deteriorating lead paint is not a contributing factor (e.g., soil contamination attributable to smelter emissions, past use of leaded gasoline, other sources), can be an equally important exposure pathway, compared with lead paint that is deteriorating in place (Mielke and Reagan, 1998). Much has been done to address all environmental lead sources, and much more needs to be done. Since 1977 the Consumer Product Safety Commission (CPSC) has limited the lead content of paint in the United States to 600 parts per million (or else 0.06% by dry weight of the paint), but older residencies may have paint present with much higher lead content (up to 50% lead before 1955; Agency for Toxic Substances and Disease Registry, 2007). The US EPA's Office of Chemical Safety and Pollution Prevention also recently issued the lead Renovation, Repair, and Painting rule to protect against exposure from renovations that disturb lead-based paint (US EPA, 2010).

After the landmark phase-out of commercial leaded gasoline, which was completed in 1995, 78% of air lead in the United States is attributed to industrial emissions (Levin et al., 2008). The US EPA has set an enforceable national quality standard for lead in ambient air, while the Occupational Health and Safety Administration has set an enforceable permissible exposure limit for lead in workplace air (Agency for Toxic Substances and Disease Registry, 2007). Lead is also present in consumer products. Dietary supplements, crystal glassware and ceramic pottery, polyvinyl chloride miniblinds, synthetic turf, imported candy and foods, and imported children's toys have been found to contain high levels of lead (Levin et al., 2008). The CPSC has recalled thousands of imported products, including children's toys, which contained lead and did not meet U.S. standards (Levin et al., 2008).

While the conventional wisdom is that lead in paint and in dust account for a majority of EBLs in U.S. children, the CDC estimated that 30% or more of present EBL cases do not have an immediate lead paint source identified (Levin et al., 2008). The US EPA (2010) recently expressed an opinion, shared by many others (Levin et al., 2008; Scott, 2009), that as other agencies and

EPA offices focus primarily on other sources of lead exposure (e.g., lead-based paint, lead in dust and soil) lead in drinking water as an exposure path is becoming a bigger percentage of a smaller number.

III. U.S. REGULATIONS/GUIDELINES FOR LEAD IN TAP WATER, AND OTHER PUBLIC HEALTH GUIDANCE

Lead and Copper Rule of 1991

The US EPA regulates public water supplies under the Lead and Copper Rule (LCR) through an action level for lead at home taps of 15 parts per billion (or else 15 μg/L; US EPA, 1991). If lead concentrations exceed this action level (AL) in more than 10% of customer taps sampled, the water utility must take measures to control plumbing corrosion and inform the public about steps they should take to protect their health (Table 2). The US EPA has also set a maximum contaminant level goal (MCLG) of zero for lead at the tap. As an MCLG, this guideline is not enforceable, but represents the optimal lead-in-water level below which there is no known or expected risk to health.

Implementation of the LCR in 1991 significantly controlled lead contamination at the tap, as evidenced by a recent review of monitoring data from homes in many large U.S. cities. The review showed that 96% of U.S. utilities were below the lead AL of 15 μg/L (US EPA, 2006a). The LCR replaced the previous standard of 50 μg/L, which was ineffective because it measured lead at the entry point to the distribution system and before contact with lead containing plumbing (Figure 1). The LCR requires sampling at homes known to have plumbing with highest potential for lead contamination, and after a minimum of 6 hr in which the sampled water has to contact the plumbing (US EPA, 1991).

Reliance on the 90th percentile lead level to determine compliance with the LCR means that there is no maximum contaminant level (MCL) for lead in consumers' water to meet the federal regulation. The US EPA explicitly acknowledged this in 1991, by stating that the AL does not determine the compliance status of a system as does an MCL, but merely serves as a surrogate for a detailed optimization demonstration. The US EPA (2006b) further clarified that the LCR is aimed at identifying system-wide problems rather than problems at outlets in individual buildings and that the 15 μg/L action level for public water systems is therefore a trigger for treatment rather than an exposure level.

To illustrate, consider actual lead-in-water data from volunteers in a large U.S. city living in homes that are not necessarily at high risk, and which would be in compliance with the LCR (i.e., 90th percentile lead in water = 10 μg/L < 15 μg/L; Figure 2). One percent of this population is exposed to over 70 μg/L lead, and 0.1% of the population is exposed to lead

TABLE 2. U.S. federal regulations and guidelines for lead in drinking water of homes and schools

Federal statute	Lead and Copper Rule (LCR) of 1991 for homes served by public water systems	Lead Contamination Control Act (LCCA) of 1988	No regulation
Applies to	- Homes and other buildings served by a public water system (~85% of U.S. homes) - Schools/day cares regulated as public water systems[a] (~10% of U.S. schools)	Schools/day cares served by a public water system (~90% of U.S. schools)	Homes with private water system (~15% of U.S. homes)
Enforceable?	Yes, federal regulation	No, voluntary guidance	Not applicable
Required sample number	5–100 taps, depending on the size of the population served (reduced to 5–50 taps, for utilities previously compliant with the rule)	Each school water outlet used for drinking and cooking	None
Sampling Frequency	every 6 months (reduced to as little as once every 3 years for utilities previously compliant with the rule)	Not specified	None
Sampling requirements	1 L cold water samples after at least 6 hr of stagnation	250 mL cold water samples after 8–18 hours of stagnation	None
Lead Limit	15 μg/L, termed "Action level" (AL)	20 μg/L	None
Failure criterion	Over 10% of samples exceeding AL of 15 μg/L lead (or else 90th percentile lead > AL)	Any water sample exceeding 20 μg/L lead	None
Remediation measures	Corrosion control optimization,lead service line replacement,public education	Flushing, point-of-use filters, remove plumbing, bottled water, public education	None
Reference	US EPA, 1991	US EPA, 2006b	US EPA, 2006c

[a]Schools that regularly provide water to at least 25 individuals per day and use their own water source (e.g., private well), or treat, or sell their water, are regulated as public water systems.

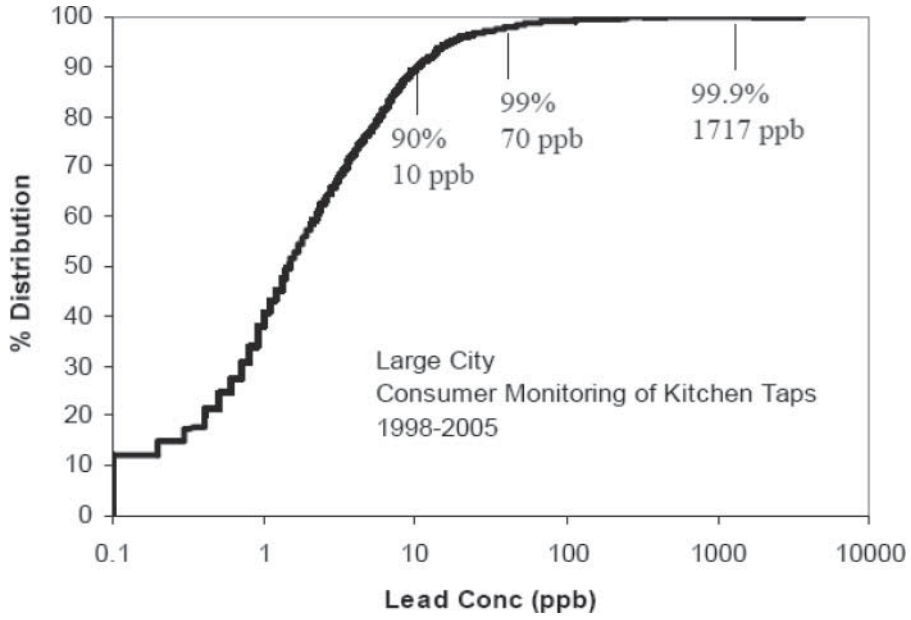

FIGURE 2. Cumulative distribution of lead-in-water levels (in logarithmic scale) at consumers' home taps in a large U.S. city from 1998 to 2005. Compiled from monitoring data of city residents, who voluntarily collected tap water samples and submitted them for lab analysis (S. Patch, personal communication, November 28, 2006).

over 1717 μg/L. If the U.S. goal of eliminating EBL in all children by 2020 is to be achieved, the higher risk at the upper tail of the WLL distribution needs to be acknowledged and remediated. Consistent with the previous points, it is not surprising that a recent case of lead poisoning was attributed to lead contaminated tap water in Durham, North Carolina, even though the city was compliant with the LCR (Triantafyllidou et al., 2007). In addition, because the LCR is designed to monitor effectiveness of corrosion control and does not protect individual consumers, only 100 homes must be tested in large cities (US EPA, 1991), which translates to far less than 1 out of 1,000 households. The key point of this discussion is that compliance with the LCR lead action level does not guarantee, or even imply, that all individuals in the city are protected from lead-in-water hazards.

Moreover, LCR testing loopholes may allow high lead levels to be missed, either accidentally or intentionally, in the relatively small number of homes that are sampled (Renner, 2009; Scott, 2009). For example, failure to pick the worst-case houses, not allowing water to stagnate long enough inside the plumbing before sampling, removing the faucet aerator screen before sampling, or sampling in cooler months can allow compliance with the LCR AL for lead, and effectively hide serious water contamination (Renner, 2009). Sampling practices that can miss lead-in-water hazards have been

employed in major U.S. cities (Leonnig, 2004), although the majority of U.S. water utilities sample tap water and report monitoring data with the safety of their consumers in mind.

Lead Contamination Control Act of 1988

The LCR also applies to the 10% of U.S. schools that have their own water supply (Table 2). However, it does not extend to the majority of U.S. schools and day care facilities, which rely on public water systems for their water supply (Table 2). Instead, the Lead Contamination Control Act (LCCA) provides nonenforceable guidelines for these schools and day care facilities, recommending that drinking water should not exceed 20 μg/L lead in any 250 mL first-draw sample (US EPA, 2006; Table 2). In other words, aside from the 10% of U.S. schools that are regulated as public water systems under the LCR due to use of their own water supply or well, the remaining 90% of U.S. schools and day care facilities are not subject to any enforceable national lead-in-water standard (Table 2).

The recommended guideline of 20 μg/L applied to lead in school water is considered more stringent than the 15 μg/L lead action level for homes, because a 250 mL water sample under the LCCA tends to concentrate the lead in collected samples, compared to the 1-L samples collected under the LCR (US EPA, 2010). Passage of the LCCA in 1988 prompted many schools to test for lead in drinking water, but state adoption and enforcement of the guideline was often weak and even nonexistent (Lambrinidou et al., 2010). By 1990 many schools had not repaired or removed lead-tainted coolers, used sampling protocols other than those recommended by EPA, carried out very limited or inappropriate sampling, or failed to conduct water testing at all (Lambrinidou et al., 2010).

A recent investigative report by the Associated Press (Burke, 2009) and subsequent congressional hearing (Freking, 2009) revealed problems with high lead in water of hundreds of schools regulated as public water systems under the LCR. In response, the EPA has stated it plans to better address and enforce lead standards in such situations (Freking, 2009). Although much less information is available for the 90% of schools not subject to any sampling requirements, case studies in Baltimore, Maryland; Seattle, Washington; Philadelphia, Pennsylvania; Washington, DC; Maryland suburbs; and Los Angeles, California, revealed serious problems with lead contamination of school water in recent years (Table 3). In the vast majority of these cases, lead-in-water hazards were not revealed by the schools under the LCCA, but by parents/students or investigative reporters (Table 3). With only one exception, at least three years elapsed from the time the schools recognized a problem to the time the public was informed. Another key point is that a large percentage of taps in some of the schools (up to 80%)

TABLE 3. Representative case studies on lead-in-water problems at U.S. schools

School system location	Year school knew of problem	Year public informed	How discovered	Average % taps above LCCA guidance of 20 μg/L*	Highest reported Pb in water (μg/L)	References
Baltimore, MD	1992	2003	Parent inquired as to why water fountains had been turned off and a teacher turned whistleblower.	20% of fountains	655	City of Baltimore, 2007 J. Williams, personal communication, July 23, 2008
Seattle, WA	1990	2003	A parent was concerned due to discolored water, collected and analyzed sample finding high lead.	1990: 33–40% 2004: 25%	1,600	Odell, 1991 M. Cooper, personal communication, July 13, 2008 Boyd et al., 2008a
Philadelphia, PA	1993	1998	A source unofficially provided lead-in-water test results to EPA, after EPA had been told to get a search warrant when requested to sample water.	2000: 38% of fountains 48% of faucets	not available but 17% of schools >100 μg/L	Fitzgerald, 2000 Bryant, 2004
Washington, DC	1987	2007	Freedom of Information Act (FOIA) requests by Virginia Tech; more than 80% of taps in some schools exceeded 15 μg/L lead[a]	2004: 4% 2006: 29% 2007: 13% 2008: 26%	2004: ***7,300*** 2006: 4,936 2007: ***20,000*** 2008: 1,987	P. Taylor, personal communication, November 2, 2007 Lambrinidou and Edwards, 2008 Lambrinidou et al., 2010
Washington Suburban, MD	2004	2004	School system voluntarily collected samples to participate in LCCA after problems were revealed in Washington, DC.	2004: 18%	***36,372***	Gerwin, 2004 Montgomery County Public Schools, 2004
Los Angeles, CA	1998	2008	Local news station; school personnel falsified daily reports regarding remedial flushing to reduce lead.	2008: 30%	Not available	Lambrinidou et al., 2010 Grover, 2008a

Note. Bold italics indicate lead-in-water levels that were high enough (i.e., >5000 μg/L) to classify the drinking water as hazardous waste, based on the Toxicity Characteristic Leaching Procedure (TCLP) test, which regulates lead in waste at a level of 5 ppm or else 5,000 μg/L (US EPA, 2009).

[a]All data from Washington DC schools in this table use 15 μg/L as a failure criterion.

had lead in water above the LCCA standard of 20 μg/L. In addition, some schools had taps dispensing water with lead levels exceeding hazardous waste criteria (i.e., >5,000 μg/L lead; Table 3).

Remedial measures in these school systems varied from replacing bubbler heads or installing new fountains to installing filters, flushing, turning off fountains, and providing bottled water (Boyd et al., 2008b; Greenwire, 2004; Grover, 2008b; Montgomery County Public Schools, 2007). These remedial measures invariably relied on a trial-and-error approach. Thankfully, some of these school systems appear to have resolved the majority of lead-in-water problems, at least in the short term. However, remediation sometimes involved millions of dollars to replace fixtures and fountains, only to have the problem return a few months later (Bach, 2005). Similar to lead paint, lead-in-water problems can never be considered fully resolved, until the lead-bearing materials have been completely removed. It is also worth noting that the schools described in Table 3 represent the good news, as most other school systems in urban areas have not systematically tested their water for lead in nearly three decades. Not shown in Table 3 are other case studies from (a) Davidson, North Carolina, where a problem was discovered after a high school chemistry experiment failed and the teacher eventually traced it to high lead in water (Edwards, 2007); (b) Durham, North Carolina, where sampling revealed hazardous lead levels in some water fountains at 8 schools (Biesecker, 2006); and (c) New Jersey (Burney and Dwight, 2003).

The limited attention on lead in drinking water of schools and day care facilities is disconcerting, given the potential public health risk. First, school children are much more vulnerable to adverse health effects from lead exposure relative to adults (Needleman, 2004). Second, the intermittent pattern of water consumption, with periods of little or no water use on weekends, holidays, and over summer break, produces very long stagnation periods of water inside the piping and can be worst case for releasing hazardous levels of lead from the plumbing into the water supply (Levin et al., 2008). Finally, school buildings have intricate plumbing systems, sometimes very old, containing multiple potential sources of water lead contamination. In 2004, the US EPA requested information and compiled a summary of state programs, regarding implementation of LCCA guidance (US EPA, 2004). More recently, acknowledging the lack of information on drinking water of schools, the US EPA (2010) announced that it is developing a draft entitled "Charge on Safer Drinking Water in Schools and Child Care Facilities Initiative" that will seek input on how to assess the risks of lead in school drinking water.

Despite these recently acknowledged problems with elevated lead in school water, one analysis that was conducted to examine the health risks suggested that there was little cause for concern. Sathyanarayana et al. (2006) simulated typical and worst-case scenarios of drinking water consumption at

Seattle schools, and predicted reassuring blood lead levels for school children of below 5.0 μg/dL in all cases. However, these authors dismissed the highest detected lead-in-water measurements as unrepresentative, and only considered the geometric mean blood lead level of the student population using a biokinetic model. It is likely that explicit consideration of the highest measured lead-in-water samples, and resultant impacts on blood lead of more sensitive children as opposed to only the geometric mean (i.e., the 50th percentile of blood lead levels), would indicate a much more serious risk. In support of this hypothesis, it was recently revealed that a child with elevated blood lead from water in Greenville, North Carolina, was exposed in a day care center (E. Robertson, personal communication, March 24, 2006), and environmental assessments in Washington, DC, attributed a child's elevated blood lead to contaminated water (7,300 μg/L lead) at an elementary school (Lambrinidou et al., 2010). Concerns related to a case of adult lead exposure for a teacher in an Oregon school in 2008 gave impetus to testing of tap water for water fountains at work, which revealed high lead in water (Y. Lambrinidou, personal communication, December 10, 2008). Reports of harmful exposure are more consistent with common sense expectations, considering that the higher levels of lead detected in some schools (Table 3) indicate that a single glass of water can contain up to 29 times more lead than that deemed to constitute an acute health risk according to the CPSC (i.e., 20,000 μg/L lead in a 250-mL sample constitutes a single dose of 5000 μg lead, while the CPSC criterion is set at 175 μg lead).

Unregulated Drinking Water Systems

About 15% of Americans operate their own private drinking water supplies (e.g., private wells and cistern type systems; US EPA, 2006c). These systems are not subject to federal standards for lead monitoring (and other contaminants), although the major lead sources are similar to those found in public water supplies (Table 2). As a result, the magnitude of lead-in-water problems at these homes and the potential public health risks have not been studied (Schock et al., 1996).

Other Public Health Guidance as It Relates to Lead Contamination of Tap Water

The LCR and LCCA lead limits were derived from an estimation of lead concentrations considered at the time economically and technologically feasible to achieve, and as such, are not entirely health based (Lambrinidou et al., 2010). A compilation of other health-based thresholds (Table 4) indicates that the US EPA MCLG for lead in water is equal to zero and that the state of

TABLE 4. Public health guidance regarding various levels of lead in tap water

Agency	Lead threshold (μg/L)	Health guidance and/or warning	Reference
U.S. Environmental Protection Agency	0	Maximum contaminant level goal (MCLG), below which there is no known or expected risk to health	US EPA (1991)
California Environmental Protection Agency	2	Public health goal (PHG) for all age groups	Cal/EPA (1997)
Health Canada	10	Maximum acceptable concentration (MAC) based on chronic health effects, for all age groups	Health Canada (1992)
World Health organization	10	Health-based guideline for all age groups	WHO (1993)
CDC	15	Children and pregnant women should not drink the water	CDC (2010a)
U.S. Environmental Protection Agency	40	Imminent and substantial endangerment to children (warning removed in 2004)	Renner (2010)
U.S. Consumer Product Safety Commission	700[a]	Acute health risk to children	CPSC (2005)
U.S. Environmental Protection Agency	5000[b]	Hazardous waste classification	US EPA (2009)

[a]Lead dose of 175 μg translated to lead exposure through water consumption of 250 mL (one glass).
[b]Based on the Toxicity Characteristic Leaching Procedure (TCLP) test for waste.

California has developed its own public health goal for lead in water at 2 μg/L. The US EPA at one time indicated that 40 μg/L lead in water poses an imminent and substantial endangerment to children (Table 4). Health Canada (1992) and the World Health Organization (1993) have both developed a health-based guideline of 10 μg/L lead for drinking water, while the CDC (2010) advised children and pregnant women to not consume water that contains more than 15 μg/L lead (Table 4). As a further point of reference, the CPSC (2005) classified a lead dose of 175 μg as an acute health risk to children. This CPSC standard was used as a trigger for recalling millions of children's toy jewelry (CPSC, 2005). If this standard, which was applied to children's jewelry and toys (products not intended for human consumption), was applied to lead in water (a product intended for human consumption), the one-time ingestion of 250 mL of water at 700 μg/L lead (resulting in a lead dose of 175 μg) would also be classified as an acute health risk to children (Table 4). Finally, water containing more than 5,000 μg/L lead exceeds hazardous waste criteria (US EPA, 2009).

IV. FORMS OF LEAD IN TAP WATER AND IMPLICATIONS FOR MONITORING AND EXPOSURE

Dissolved Versus Particulate Lead in Tap Water

Lead that is released from plumbing into drinking water can be present in a variety of distinct physicochemical forms including free aqueous ions, inorganic complexes, organic complexes, associations with highly dispersed colloidal matter, suspended particles of insoluble salts, or adsorbed on inorganic particulates (De Rosa and Williams, 1992). In some practical tests, the total lead content of drinking water is often demarcated into two fractions: the dissolved lead fraction and the particulate lead fraction (Table 5). Dissolved lead is operationally defined as the fraction of total lead in water that is small enough to pass through a filter of 0.45-μm pore size (McNeill and Edwards, 2004). Particulate lead is the fraction of total lead in drinking water that is retained by a filter of 0.45-μm pore size (Table 5). At the upper end of particulate lead sizes, these particles are big enough to be seen by the naked eye.

Lead particles in tap water can originate from detachment of lead-bearing scale or rusts from plumbing, or by scouring/sloughing-off during water flow (Schock, 1990). Lead corrosion rusts in water plumbing materials are analogs of peeling lead paint, in that degradation of the underlying plumbing material can dramatically increase the creation of these particles, their detachment, and resulting human exposure. Indeed, the mineralogical forms of many lead rusts (i.e., cerrusite and hydrocerrusite; see Table 5) are

TABLE 5. Classification of lead species in tap water and distinction between dissolved lead and particulate lead (adapted from De Rosa and Williams, 1992)

Operational definition	Approximate diameter size (μm-log scale)	Class	Example(s)
Dissolved lead		Free aquo ions	Pb^{+2}
	0.001	Organic chelates, other inorganic ions, ion pairs and complexes	Pb-EDTA $PbCO_3$
	0.01	Bound to macromolecules	Pb-fulvic acid complexes
	0.1	Highly dispersed colloidal material	Adsorbed on hydrous iron and manganese oxide colloids
0.45		Adsorbed on inorganic particulates	Adsorbed on hydrous iron and manganese oxides and clay minerals
Particulate lead	10+	Minerals and precipitates	$PbCO_3$(s)-Cerussite $Pb_3(CO_3)_2OH_2$(s)-Hydrocerussite

identical to those in lead paint. Lead particles in tap water may also originate from physically degraded pieces of leaded brass, lead solder, or lead pipe (Triantafyllidou et al., 2007). Unlike the case of dissolved lead in water, which is not controlled by nuances of water flow from the tap, the mobilization of particulate lead from plumbing can be highly variable, depending on changes in pressure and water flow velocity/direction (Schock, 1990).

Numerous investigators have reported lead particles in water. Flaking lead particles larger than 12 μm in diameter were observed detaching from pipe, along with colloidal lead fractions associated with iron oxides and humic acids (De Mora et al., 1987; De Rosa and Williams, 1992). An extensive British survey reported that the flaking lead problems were caused by large black/brown particles visible to the consumer, whereas colloidal lead problems were caused by smaller particles that were not visible (De Rosa and Williams, 1992). The British report further concluded that problems with particulate lead were often associated with the presence of iron particulates, and that these problems were exacerbated by high water flows, especially during periods of high water demand (i.e., in the summer), as was recently highlighted in the United States (HDR Engineering, 2009).

A small survey of lead in potable water from around the United States revealed numerous instances in which lead was also present as particulates, sometimes at concentrations greater than 1,000 μg/L (McNeill and Edwards, 2004). Particulate lead was also clearly demonstrated to detach from lead-tin solder joints (Bisogni et al., 2000) and from lead pipes (Triantafyllidou et al., 2009a) in laboratory test rigs. In these laboratory studies, particulate lead was the predominant form of lead, comprising up to 99% of the total lead concentration in water samples (Triantafyllidou et al., 2009a).

Field investigations at various U.S. locations with significant lead-in-water problems revealed that particulate lead release from the plumbing was often the cause (Figure 3; Table 6), and in some cases the source of the lead problem could be forensically linked to either lead pipe, lead solder, or leaded brass (Table 6). A key point is the extraordinarily high levels of lead (up to 190,000 μg/L, or else more than 12,000 times the EPA AL) occasionally present in the water due to these particles, and their varying mineralogical content ranging from 3% to 100% lead (Table 6). The massive lead contamination occasionally resulting from partial lead pipe replacements is especially noteworthy, in light of the CDC report of EBL in Washington, DC, children (Frumkin, 2010).

Implications of Particulate Lead in Tap Water for Monitoring, Exposure Assessment, and Corrosion Control

Chemical lead solubility models, human exposure models, water sampling protocols, and analytical quantification methods are often based on the presumed dominance of dissolved lead in drinking water. It has only recently

TABLE 6. Origin of representative lead particles identified in drinking water during field investigations, and level of resulting water contamination

Location of case study	Surface composition of lead-bearing particle(s)	Origin of lead particle(s)	Total Pb concentration in water (federal standard is 15 μg/L)	Documented lead poisoning?	Reference(s)
University of North Carolina at Chapel Hill, NC	3–22%Pb, 26–66% Cu 4–40% Zn (3–19% Fe, 0% Sn)	Leaded brass	Up to 350 μg/L	No	Elfland et al. (2010)
Greenville, NC	4–51% Pb 1–70% Sn (0–6% Cu)	Lead solder	Up to 10,500 μg/L	Yes	Triantafyllidou et al. (2007)
Durham, NC	17–52% Pb 37–66% Sn	Lead solder	Up to 650 μg/L	Yes	Edwards et al. (2006)
Raleigh, NC	3% Pb 97% Sn	Lead solder	2,413 μg/L	No	Parks and Edwards (2008)
Manchester, ME	Pb and Sn (levels not specified)	Lead solder	Up to 3,200 μg/L	Yes	Edwards (2006)
Washington, DC (after partial lead service line replacement)	Unknown, but presumably metallic lead (i.e., 100% Pb) and lead rusts	Lead service line	Up to 190,000 μg/L	Yes	Frumkin (2010) DC WASA (2008)
Washington, DC	63% Pb 37% Sn	Lead solder	Not available	No	Edwards (2005)
Washington, DC	Not analyzed	Lead solder, leaded brass	Up to 974 μg/L[a]	Yes	Edwards (2008)
Washington, DC, Suburban Area	1.6–9.9% Pb, 60–79% Sn, 1.8–5.0% Cu	Lead solder, leaded brass	Up to 1,403 μg/L[a]	No	Edwards (2006)
Small Community, TN	Not analyzed	Lead solder, confirmed onsite via spot test	Up to 2,886 μg/L	No	Edwards et al. (2007)

[a]Aside from lead and tin presence, high amounts of copper and zinc in water samples suggested that brass was also contributing to the problem.

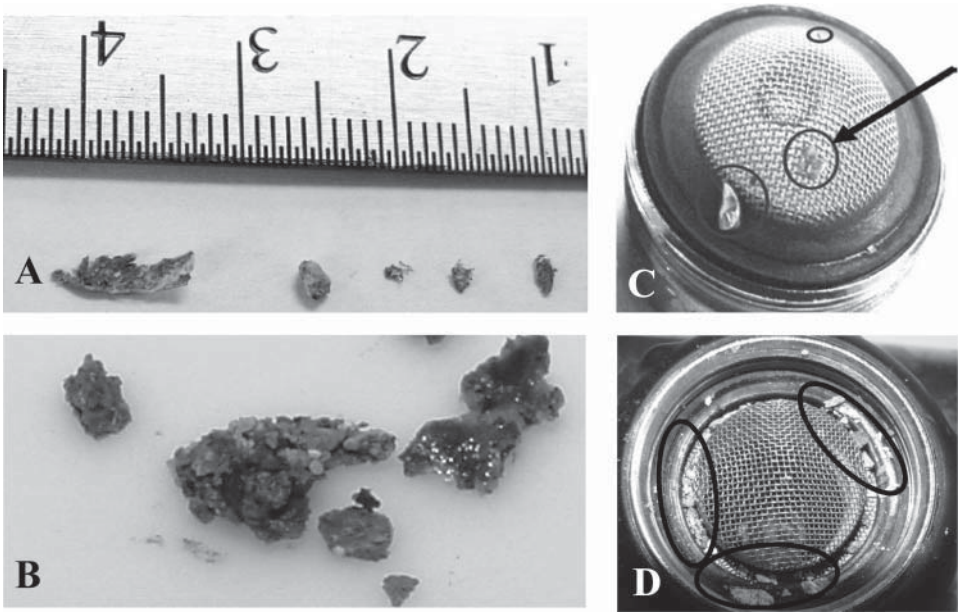

FIGURE 3. Lead-bearing particles were identified as the cause of severe tap water contamination during field investigations. (A and B) Brass particles trapped in two different strainers adjacent to two drinking water fountains at the University of North Carolina at Chapel Hill (Elfland et al., 2010). (C) Lead solder particles trapped in home faucet aerator screen in Washington, DC (Edwards, 2005). (D) Lead solder particles trapped in home faucet aerator screen in Greenville, North Carolina (Triantafyllidou et al., 2007).

been recognized that particulate lead can occasionally be the dominant form of lead in drinking water (Triantafyllidou et al., 2007). A preliminary synthesis (Table 6) indicates that such problems may not be an isolated occurrence, especially given the rarity of such measurements.

It is useful to highlight some of the challenges associated with the presence of particulate lead in tap water, in terms of environmental monitoring and exposure. All models predicting lead at the tap do so by considering soluble lead (Schock, 1990). Because the release of particulate lead in drinking water is often caused by physical factors and is erratic, its contribution is impossible to predict (Schock, 1990). At the same time, capturing actual particulate lead spikes in tap water via field sampling is very challenging. Schock et al. (2008) warned that if lead (and other contaminants) were mobilized into solution or released as particulates, this would result in long-term intermittent exposures of unknown impact that can easily go undetected.

Particulate lead in water can be ingested and subsequently be dissolved or mobilized by human stomach acid (Schock, 1990). Mahaffey (1977) reported that lead absorption from small lead particles is greater than lead absorption from large particles. However, she also reported that when large pieces of lead are ingested, they may lodge in the gastrointestinal tract and

cause severe lead poisoning as they slowly dissolve. Bioavailability tests on lead solder particles collected from homes of lead-poisoned children in Greenville and Durham, North Carolina, revealed that a significant fraction of the particulate lead from solder dissolved in simulated gastric fluid (Triantafyllidou et al., 2007). Additional case studies of childhood lead poisoning in Maine and in Washington, DC (Table 6), which were attributed to lead-baring particles that detached from the plumbing and contaminated tap water, also provide unambiguous proof that these lead particles were indeed bioavailable once ingested.

In order to protect consumers from such exposures, corrosion control programs need to account for and prevent particulate lead release into the water. Modern corrosion control strategies were designed to reduce leaching from lead pipe, solder, and brass materials by encouraging formation of low solubility lead hydroxyl-carbonate and phosphate films on the plumbing material surface, which can limit contamination to flowing water. But control of particulate release is dependent on minimizing the destabilization of the protective rust layer from water quality changes or hydraulic disturbances, and this process is poorly studied. The drinking water industry presently lacks the tools or knowledge to completely prevent or control particulate lead release.

V. BLOOD LEAD LEVEL AND MAJOR LEAD TOXICITY MECHANISMS

Potential harm from exposure to lead is typically tracked by measurements of the BLL. BLLs above 10 μg/dL are considered elevated (EBLLs) for infants and children, as they exceed the CDC threshold at which detectable mental impairment and behavioral changes have been documented (CDC, 2005). Cases in which blood lead exceeds 10 or 20 μg/dL are also termed *lead poisoning*, dependent on the specific U.S. jurisdiction. CDC surveillance for the year 2007 corresponded to only 13% (or else 3,136,843) of U.S. children aged <6 years, of which 31,524 were diagnosed with EBLL (CDC, 2010).

Depending on the extent of uptake by the blood stream (Table 7), lead disturbs the heme biosynthetic pathway and can lead to anemia (Singhal and Thomas, 1980), causes kidney malfunction or even kidney failure (Loghman-Adham, 1997), but most importantly generates brain disorders in children (Needleman, 2004). Lead is a neurotoxin, which has the capacity to enter the blood-brain barrier and affect the central nervous system of children (National Research Council Board on Environmental Studies and Toxicology, 1993). Nerve signaling is highly regulated by movements of charged ions, such as calcium, across cell membranes. At picomolar concentrations lead (Pb^{+2}) outcompetes/inhibits calcium (Ca^{+2}) from entering cells, halts release of neurotransmitters from the cell, and thus disrupts nerve signaling

TABLE 7. Blood lead level (BLL) and adverse health effects in children and in adults

	Age group	
	Children	Adults
BLL (μg/dL)		
<10	IQ (−), hearing (−), growth (−)	Uncertain
>10	Erythrocyte protoporphyrin (+)	Hypertension
>20	Nerve conduction (−)	Erythrocyte protoporphyrin (+)
>30	Vitamin D metabolism (−)	Systolic blood pressure (+) Hearing (−)
>40	Hemoglobin synthesis (−)	Nerve conduction (−), infertility (men), kidney failure
>50	Colic, frank anemia, kidney failure, brain disorders	Hemoglobin synthesis (−) frank anemia, brain disorders
>100	Death	Death

Note. The BLL of concern is presently set at 10 μg/dL. Adapted from Troesken (2006) and National Research Council Board on Environmental Studies and Toxicology (1993). Hemoglobin is the molecule which carries oxygen throughout the body. Nerve conduction is ability to send the impulse from the nerve to the muscle. Vitamin D is necessary for the absorption of calcium and phosphorus, and for bone growth. Erythrocyte protoporphyrin is the intermediate in heme biosynthesis. (−) = decreased function; (+) = increased function.

(Needleman, 2004). Encephalopathy (i.e., brain disorder) due to elevated lead burden has been associated with lower intelligence scores (IQ), learning disabilities, hyperactivity, attention deficit disorders, hearing/speech impediments, seizures, and behavioral impairments/aggression, while some ecological studies even support an association with crime (Needleman, 2004). In addition, lead is considered an embryo-fetal poison for pregnant women, which at high levels has been historically associated with instantaneous abortion, premature delivery, stillbirth, infant mortality, low birth weight, and compromised mental and physical development of infants (Mahaffey, 1985; Troesken, 2006, 2008).

Recent studies suggest that decreased IQ and cognition occur in children even at BLLs as low as 3.0 μg/dL (Bellinger and Needleman, 2003; Jusko et al., 2008), and that impaired kidney function occurs in adolescents even at BLLs as low as 1.5 μg/dL (Fadrowski et al., 2010). Emerging clinical evidence is therefore strongly reinforcing the notion that no safe level of lead exposure exists. Lead toxicity (Table 7) is notoriously difficult to diagnose, and creates a wide range of symptoms which are easily overlooked (Kalra et al., 2000). In light of these and other evidence, the U.S. Department of Health and Human Services (2000) established the ambitious goal of eliminating EBLLs in U.S. children by 2010. This was a qualitatively different goal from earlier policy, which focused on reducing the BLL considered toxic by various target amounts (CDC, 2005). Meeting the Healthy People 2010 objective to

eliminate EBLLs (i.e., BLLs $\geq$ 10 μg/dL) in children was not achieved, and the United States is extending this goal to 2020 (U.S. Department of Health and Human Services, 2010).

VI. IMPORTANT CONSIDERATIONS IN ASSOCIATING LEAD IN WATER TO LEAD IN BLOOD

Troesken (2006) acknowledged that exposure to water lead is subject to an error-in-variables problem, which makes it challenging to find an association to health risks, and introduces a downward bias into commonly applied statistical techniques attempting to link WLLs to BLLs. In order to avoid such a bias, it is necessary to meet several preconditions when attempting to associate BLLs to WLLs in population studies or in case studies:

- Water lead measurements and blood lead measurements need to be available, and without significant sampling delays between the two;
- Water lead measurements need to quantify the actual lead content of the water;
- Individual water consumption patterns need to be accounted for; and
- Individual responses to the same lead dose need to be understood.

Some of the difficulties in meeting the above criteria (Table 8) are highlighted in this section.

Paired BLLs and WLLs Are Not Always Available

It is obviously necessary to obtain BLL and WLL data, in order to examine any potential association between the two. For a variety of reasons (Table 8) described subsequently, such data are often unavailable.

Lack of BLL Data for Sensitive Subpopulations

In the United States children's blood lead screening is targeted to children at highest risk for exposure to lead paint and lead dust hazards (CDC, 2002), typically aged 1–6 years with developed hand-to-mouth activity (Linakis et al., 1996). Relatively little data is available for children aged less than 9 months, who are most vulnerable to lead exposure through water, due to use of reconstituted milk formula (Edwards et al., 2009; Shannon and Graef, 1992).

General Lack of WLL Data at Schools and Day Care Facilities

As of 2006, a survey by the CDC found that nearly half of all schools nationwide do not test their water for lead (Lambrinidou et al., 2010). A 2006

TABLE 8. Potential difficulties in associating lead in water to lead in blood in population studies or in case studies

Issue	Illustrative reference(s)
BLLs and WLLs are not always available	
General lack of BLL measurements for sensitive sub-populations	Binder et al., 1996 Shannon et al., 1992
General lack of WLL measurements in schools/daycares under the LCCA	Edwards et al., 2009 Lambrinidou et al., 2010
Relatively small number of WLL measurements under the LCR	Renner, 2009
Relative exclusion of water lead measurements during home assessments of lead-poisoned children	Renner, 2009 Scott, 2009
WLL measurements do not always reflect actual lead in water	
Improper water sampling/preservation methods at "high-risk" taps under the LCR - Flow rate - Cold versus hot water - Sample preservation	Triantafyllidou et al., 2007 Triantafyllidou et al., 2009
Inherent variability in lead release from plumbing - Spatial (fluctuations within a city, a neighborhood, or even a single home) - Temporal (fluctuations in a single tap depending on season, or even time of day)	Levin, 2008 Schock, 1990 Matthew, 1981
Individual water consumption patterns affect individual exposure	
Variability in individual water consumption patterns - Amount of water consumed in/outside of home - Use of tap/filtered tap/bottled water	Troesken, 2006 Matthew, 1981
Underestimated indirect contribution of water to the total dietary lead intake - Preparation of foods and beverages	Triantafyllidou et al., 2007 Mesch et al., 1996 Moore, 1983
Individual risk factors affect individual response to a fixed lead dose	
Bioavailability of lead varies between individuals, depending on - Age - Diet - Genetics	Troesken, 2006 Lanphear et al., 2002 Matthew, 1981

analysis by the U.S. Government Accountability Office revealed that few states have developed voluntary comprehensive testing and remediation programs for lead in school drinking water, and that about half the states have not developed programs at all (Lambrinidou et al., 2010). A recent nationwide Associated Press survey on the 10% of U.S. schools that are subject to the LCR revealed that lead-contaminated drinking water affects schools in at least 27 states (Lambrinidou et al., 2010). There is no scientific or practical reason to believe that the problem does not extend to other schools and to other states, which are not being monitored for lead-in-water problems.

Relative Exclusion of Water Lead Measurements During Assessments of Lead-Poisoned Children

Management strategies for childhood lead poisoning in the United States have been developed based on the assumption that the LCR eliminated elevated water lead and that other environmental sources (e.g., lead in paint, dust, or soil) are the most likely culprit. Present CDC guidance states that if prior testing of a public water system shows that lead contamination is not a problem in homes served by that system, no additional testing is necessary, unless no other source of a child's EBLL can be found (CDC, 2002). Public health agencies routinely misinterpret compliance with the LCR action level as eliminating the need for water sampling in homes, schools, or day care facilities of lead-poisoned children.

A Virginia Tech survey in 2006 verified that drinking water sampling is not standard practice during home assessments of lead-poisoned children. From the 17 states that responded to the survey, only two required water testing in all cases of EBLL. Three of the jurisdictions often tested the water, eight of the jurisdictions sometimes tested the water, and four said they never did. A follow-up survey by the Alliance of Healthy Homes (Scott, 2009) revealed that in a state with a severe lead-poisoning rate water is tested when no lead paint violations are identified, but this is virtually never. Another state with similar problems claimed to occasionally test the water if it's the only way to convince the parents that the real hazard is lead-based paint in their home (Scott, 2009). A different survey by the CDC (Renner, 2009) showed that 15 lead grantee municipalities routinely collected water samples during home inspections, and that 16 sometimes sampled drinking water (if lead was not found in paint or dust, or if drinking water was provided by a private well or unregulated water system), while seven never tested drinking water.

Even when sampling is conducted, the CDC does not provide specific guidance on when and how to test water for lead (Renner, 2009). If a water sample is taken at all, it is typically a flushed sample taken during the inspection. This means that in the few instances where health agencies do collect tap water at homes of lead poisoned children, they are usually not collecting worst-case samples, and are thus not capturing worst-case lead-in-water exposures (Renner, 2009).

WLL Measurements Do Not Always Reflect Actual Lead in Water

In order to assess the public health risk from elevated lead in tap water, it is obviously necessary to first measure the actual lead content of the water. But lead-in-water measurements can be controlled by the season, day, hour of measurement, and subtle differences in sample collection procedures can either detect or completely miss lead spikes (Table 8).

Improper Water Sampling/Preservation Methods at High-Risk Taps May Miss Some of the Lead Present in Water

Standard sampling/analytical protocols are adequate in quantifying lead in water in the typical case. In exceptional cases (e.g., when childhood lead poisoning may be caused by water) the detection of lead hazards can be critically dependent on the specifics of sampling.

Flow Rate During Sample Collection. The most recent guidance for schools (US EPA, 2006b) suggests to induce a small (e.g., pencil-sized) steady flow of water from the outlet. These instructions translate to an unrealistically low flow rate of less than 1 L/min. Yet everyday water consumption typically employs higher flow rates, at which it has been long known that the water may physically scour lead deposits from the pipe (Britton and Richards, 1981; Schock, 1990). Sampling at a higher flow rate would therefore more likely capture lead spikes due to particulate lead release, and would be more representative of typical water usage. Collecting water from a high-risk tap at the US EPA-recommended low flow rate missed 90% of the particulate lead present (Edwards, 2005), during a home investigation in Washington, DC, in 2006 (Figure 4).

Sampling of Hot Versus Cold Water. Existing protocols under the LCR and lead poisoning case management only require sampling of cold tap water. Instead of sampling hot tap water, which is occasionally known to contain much higher lead, the USA EPA (2006b) simply recommends that consumers never drink hot water or use it for cooking. A case study in Australia, where three individuals were diagnosed with lead poisoning, revealed

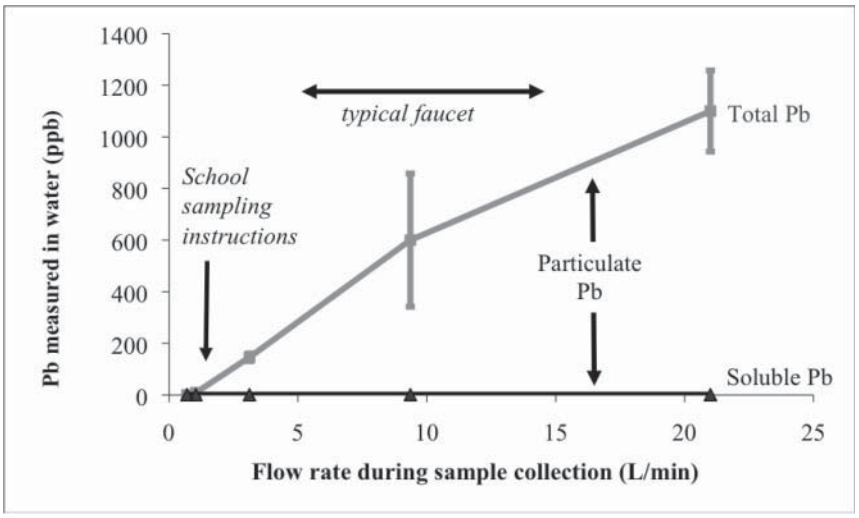

FIGURE 4. Lead measurement in flushed tap water samples versus flow rate in a home with lead pipe. Error bars represent 95% confidence intervals over triplicate samples collected on subsequent days at each indicated flow rate. Sample collection at the kitchen tap was timed to collect water derived from the lead pipe (Edwards, 2005).

that hot tap water contained 260 times more lead than did cold tap water (Mesch et al., 1996). The family members used hot water to prepare instant coffee and to cook. In another Australian study, water was collected from water boilers and coffee machines from restaurants, offices, workplaces, and schools. Excessive levels of lead were found in 67% of the samples, probably due to the contact of brass components with the hot water (McCafferty et al., 1995). In Washington, DC, review of environmental risk assessments in the homes of children with elevated BLLs during 2006–2007 revealed that more than 50% of caregivers who were asked stated that they used unfiltered hot tap water to mix infant formula, powdered milk, and juice (Lambrinidou and Edwards, 2008). Clearly, individuals consume hot tap water even though advised not to, and this risk is not quantified.

Sample Preservation. Existing analytical methods are based on the assumption that lead in water is dissolved, and that standard preservation of water samples at pH $\leq$ 2.0 with addition of 0.15% nitric acid is adequate for detecting all the lead that is present in the water. Digestion of samples with heat or stronger acid is not required unless turbidity exceeds certain thresholds (US EPA, 1994). Edwards and Dudi (2004) first showed that the standard US EPA preservation protocol can sometimes miss much of the lead that is actually present in water. For instance, water samples actually containing 508 μg/L lead in Washington, DC, only measured as 102 μg/L, using the standard preservation protocol (Edwards and Dudi, 2004). The reason for the discrepancy is that particulate lead can settle or adhere to the plastic sampling containers, and is missed when aliquots are taken for that measurement (Triantafyllidou et al., 2007).

Inherent Variability in Lead Release from Plumbing Cannot be Captured by Single-Sample WLL Measurements

Due to spatial and temporal variability in lead release from plumbing, especially in the case of particulate lead, surveys based on a single water sample may be inadequate to characterize exposure (Matthew, 1981; Pocock, 1980). Yet present monitoring programs under the LCR or the voluntary LCCA are based on a single water sample from each outlet, due to practical and financial constraints. Schock (1990) warned that if water monitoring programs do not account for this inherent variability, then the measurements will be unrepresentative and irreproducible.

Spatial Variability. Lead-in-tap water fluctuations are possible within a city (see Figure 3), a neighborhood, or a single home, even if water is collected under a standard protocol. For example, infrequent water consumption in municipal buildings or in schools, with periods of little or no usage during weekends and breaks, results in long stagnation periods of the water inside the piping and causes it to undergo chemical changes (Levin et al., 2008). This translates to more variability in the lead concentration, compared with homes where water consumption is much more frequent and regular. In addition, pH or other chemical fluctuations, depending on how far from

the treatment plant water is transported in order to reach consumer's taps, also affects its corrosivity to leaded plumbing. Physical factors, such as the several interconnecting lines within a household plumbing system that route water to exterior faucets/bathrooms/kitchens/utility rooms and the presence and type of leaded plumbing (e.g., leaded solder, leaded brass faucets, lead pipe) greatly affect lead levels at the tap (Schock 1990).

Temporal Variability. Fluctuations in lead levels from a single tap, depending on season or even on time of day, are possible. Seasonal fluctuations in temperature and chemical constituents, as well as seasonal variations in chlorination practice by the water utility may cause variable corrosivity of the water entering a household plumbing system (Schock 1990). In the course of one day, first-draw water, drawn from a tap in the morning after overnight stagnation, is considered worst case in terms of lead release from the plumbing. Flushed water, or water collected after short holding times, tends to contain lower lead levels. Pocock (1980) argued that whatever type of water sample is collected, a single sample cannot provide a reliable estimate of the resident's exposure to water lead. To illustrate, during an environmental assessment of a lead-poisoned child in Washington, DC, in 2004, the DC Department of Health concluded that drinking water was not a potential hazard, based on collection of a single flushed water sample, which measured lead at a reassuring concentration of 11 μg/L. The Freedom of Information Act (Edwards, 2005) requests revealed that in four other flushed samples collected by the local water utility, lead in water ranged between 19 and 583 μg/L (Table 9). The samples collected by the utility provided strong indication that elevated lead in water was a potentially serious hazard, but the health agency sampling failed to make that connection based on their collection of a single flushed sample.

Individual Water Consumption Patterns Affect Individual Exposure

Variability in Individual Water Consumption Patterns

In oversimplified terms the individual risk from lead-contaminated drinking water, or any other hazard, is also a function of exposure to that hazard.

TABLE 9. Repeated flushed tap water sampling results from home of lead-poisoned child in Washington, DC. Data obtained through freedom of information act requests (Edwards, 2005).

Date	Lead determination (μg/L)	Sampling conducted by
7/26/2003	75	Water utility
3/23/2004	19	Water utility
3/23/2004	11	Department of Health
10/8/2004	21	Water utility
11/2/2004	583	Water utility

Prior research has demonstrated a strong dependence between the quantity of tap water consumed and overall exposure. For example, Potula et al. (1999) found that Bostonians who consumed medium or high levels of tap water (≥1 glass/day) that contained greater than 50 μg/L of lead developed progressively higher patella lead levels later in life, compared with those Bostonians with low levels of ingestion of the contaminated water (<1 glass/day). Similarly, Galke et al. (2006) determined that the more glasses of tap water consumed, the higher the chance of an elevated blood lead level for children in Milwaukee and in New York. Consumption of two glasses of tap water per day corresponded to a very high (50%) probability of having elevated blood lead (Galke et al., 2006).

Individual water consumption patterns may vary markedly between different age groups, and should be taken into consideration when assessing potential exposure. For instance, a Canadian survey on drinking water intake showed that infants less than 1 year old consumed on average 122 mL/kg of water a day if they were formula fed. This amount is about 3 times higher than the 44 mL/kg a day intake proposed by US EPA (Levallois et al., 2008). These authors concluded that due to their high water intake on a body weight basis, formula-fed infants may be particularly susceptible to water contaminants (Levallois et al., 2008).

The use of tap, filtered tap, or bottled water also has an obvious impact. During the Washington, DC, lead-in-water crisis, BLLs were measured in residents of homes with water lead levels greater than 300 μg/L. All residents had BLLs lower than the CDC levels of concern (10 μg/dL for children and 25 μg/dL for adults), which was at first interpreted as indicating that the high lead in water was not harmful (Stokes et al., 2004). However, later analysis revealed that only a few individuals (and no children) had been consuming tap water for months prior to having their blood lead collected, and that virtually all were using lead filters and bottled water (CDC, 2010b; Edwards et al., 2009; Edwards, 2010). The key takeaway message from the 300 μg/L study is that use of water filters, bottled water, or even flushing can be very effective at mitigating risk. Another study found that tap water can remain a significant lead exposure source through adolescence, with teens consuming bottled water having lower blood lead levels (BLLs) than those served by well or public water systems (Moralez et al., 2005).

Underestimated Indirect Contribution of Water to the Total Dietary Lead Intake

The potential for massive accumulation of lead in food during cooking is not commonly realized. Use of relatively large quantities of water to boil vegetables, pasta, or other food, and effective concentration of the lead into food via adsorption has been demonstrated (Baxter et al., 1992; Little et al., 1981; Moore, 1983). Specifically, vegetables can absorb 90% or more of the lead from the water they are cooked in (Moore, 1983). Smart et al. (1981)

showed that lead-in-water concentrations of 100 μg/L could contribute 74 μg/day of lead to the total dietary lead intake from vegetables and beverages, and at a total lead-in-water concentration of 500 μg/L the contribution was 378 μg/day. Green vegetables, carrots, rice, and spaghetti concentrated more lead than many other foods (Smart et al., 1983). While humans generally absorb lead from drinking water more readily (30–50%) than lead from food (10–15%; US EPA, 1986), the concentration effect can outweigh the reduced absorption factor. In addition to the report by Mesch et al. (1996), in which an Australian family was poisoned by use of lead-contaminated hot tap water to prepare instant coffee and cook meals, two cases of childhood lead poisoning occurred from contaminated water, even when the children did not directly consume the water. In both cases, cooking of pasta, rice, or potatoes was implicated as the source of the children's lead poisoning (Copeland, 2004; Triantafyllidou et al., 2007).

Individual Risk Factors Affect Individual Response to a Fixed Lead Dose

Variations in age, diet, and genetics will produce a range of health effects in a population, in response to a fixed lead dose from water (or other sources).

Age. The gastrointestinal absorption rate of ingested lead is inversely related to age. The typical lead absorption rate for infants is 50%, compared with just 10% in adults (World Health Organization, 2000).

Dietary Habits. Diets low in calcium or in iron, inadequate total calories, and infrequent meals are believed to be associated with enhanced absorption of ingested lead (Shannon, 1996). In dietary experiments with 23 adult volunteers, the lead retention from consumption of lead acetate was controlled by the type and timing of meals and beverages (James et al., 1985). Another study determined that subjects absorbed up to 50% of the lead on an empty stomach, 14% of the lead was absorbed when taken with tea or coffee, and 19% of the lead when taken with beer (Heard et al., 1983). Much lower uptakes ($\geq$7%) were reported when lead was ingested in the course of a meal or with large amounts of calcium or phosphate (Heard et al., 1983).

Genetics. Genetic differences may result in different individual patterns of lead uptake and biokinetics (US EPA, 2002). An increasing body of evidence suggests that tiny differences in the DNA sequence can modify the uptake, distribution, and elimination of lead by the body. For example, a 1991 study of lead workers in Germany and of environmentally exposed children in New York showed that small differences in two genes affected the absorption and excretion of lead by the participants (Wetmur et al., 1991). Another 2000 study that was performed in the Republic of Korea, with the participation of lead workers as well as persons without occupational lead exposure reached similar conclusions (Schwartz et al., 2000).

VII. SUMMARY OF STUDIES ON THE ASSOCIATION BETWEEN LEAD IN WATER AND LEAD IN BLOOD

The contribution of drinking water lead to the body's lead burden (i.e., blood lead) is a subject of an extensive body of literature, which at first glance can appear contradictory. Marcus (1986) synthesized relevant studies as part of a broader evaluation of lead health effects from drinking water, and an update of that synthesis is undertaken herein. Various approaches have been used throughout the years in population studies, in an attempt to correlate WLLs to BLLs (Table 10). These include, but are not limited to, the following:

- Focus on the most sensitive age groups (e.g., formula-fed infants, young children, pregnant/breast-feeding women) versus lumping different age groups together;
- Different types of tap water sampling to capture actual lead intake through water consumption versus utilization of available water lead data from other sources;
- Parametric correlations (assuming normal distribution of WLL and BLL) versus nonparametric correlations;
- Linear regression models versus curvilinear models to fit the original WLL and BLL data, or regression after logarithmic transformation of the original data;
- Exclusive focus on the contribution of WLL to BLL versus contribution of other environmental lead sources (e.g., lead in paint, dust, soil) to BLL as well; and
- Association between WLL and BLL versus association between WLL and percentage of study population with EBLL.

Few studies are directly comparable, but nonetheless critically evaluating the available literature provides useful insights.

Studies That Found an Association Between WLL and BLL

Association Between WLL and BLL in Formula-Fed Infants

For infants and young children up to 5 months of age, milk, formula, and drinking water are considered highly significant sources of exposure to lead (World Health Organization, 2000). In fact, for bottle-fed infants using reconstituted formula with tap water, about 90% of their diet by weight is actually tap water, as formula is typically prepared by adding 8 parts of water to 1 part of powder (Sherlock and Quinn, 1985). Additionally taking into account that the typical lead absorption rate for infants is 50%, compared to just 10% in adults (World Health Organization, 2000), elevated lead in water is

TABLE 10. Representative population studies on the association between lead in water and lead in blood (in chronological order)

Sample population	Independent variable(s)	Dependent variable	Measure of association	Model	Reference
Different sectors of Scottish population ($n = 949$)	First-draw water lead (μg/L)	Blood lead level (μg/dL)	$R = 0.52$	$BLL = 11.0 + 2.36(WLL)^{1/3}$ (units adjusted)	Moore et al., 1977
Individuals in greater Boston ($n = 524$)	First-draw water lead (mg/L), other variables such as age, sex, education, dust lead	Blood lead level (μg/dL)	Model explains 19% of variance	$Ln(BLL) = 2.73WLL - 4.70WLL^2 + 2.17WLL^3$ + other terms for age, sex, education, dust [WLL was best predictor]	Worth et al., 1981
Mothers in Ayr, Scotland ($n = 114$)	Kettle water lead (μg/L)	Blood lead level (μg/dL)	$R^2 = 0.56$	$BLL = 4.7 + 2.78(WLL)^{1/3}$	Sherlock et al., 1984
Mothers in Ayr, Scotland ($n = 114$ from 1980–81, $n = 116$ from 1982–83)	Kettle water lead (μg/L)	Blood lead level (μg/dL)	$R^2 = 0.65$	$BLL = 5.6 + 2.62(WLL)^{1/3}$	Sherlock et al., 1984 Moore et al., 1985
Women in Wales ($n = 192$)	Kettle water lead (μg/L) Air lead ($\mu g/m^{-3}$) Dust lead (μg/g)	Blood lead level (μg/dL)	Model explains 38% of variance	$Log(BLL) = 1.06 + 0.62(WLL)^{1/3} + 0.18Log(ALL) - 0.02Log(DLL)$	Elwood et al., 1984
Bottle-fed infants in Scotland ($n = 93$)	Composite kettle water lead (μg/L)	Blood lead level (μg/dL)	$R = 0.57$	$BLL = 14 + 0.062WLL$ $BLL = 15.6 + 0.052WLL$ $BLL = 14.7 + 0.054WLL$ $BLL = 15.4 + 0.052WLL$	Lacey at al., 1985 World Health Organization, 2000
Adults in Vosgian Mountains, France ($n = 155$ men, $n = 166$ women)	Tap water lead after 5 s of flushing (mg/L)	Blood lead level (μg/dL)	Spearman's $\rho = 0.30$ for men and 0.47 for women	Not determined	Bonnefoy, et al., 1985
Children in Edinburgh, Scotland ($n = 397$)	Tap water lead (μg/L), dust lead (μg/g)	Blood lead level (μg/dL)	Model explains 43% of variance	$Log(BLL) = 0.5Log(5326 + 103WLL + 3.81DLL)$ [WLL was best predictor]	Raab et al., 1987
Different sectors of population in Hawaii, with rain catchment systems ($n = 384$)	Tap water lead (μg/L), other water-related terms, other terms for soil and demographics	Blood lead level (μg/dL)	linear model explains 77% of variance	Linear model: $BLL = 5.62 + 0.025WLL + 0.0008(GLASSES*WLL) - 0.017(FILTER*WLL)$ + other terms related to water, soil, age, sex, ethnicity etc.	Maes at al., 1991

(Continued on next page)

TABLE 10. Representative population studies on the association between lead in water and lead in blood (in chronological order) *(Continued)*

Sample population	Independent variable(s)	Dependent variable	Measure of association	Model	Reference
Citizens of Sante-Agathe-des-Monts, Québec, Canada ($n = 72$)	Average water lead from 6 samples (mg/L) and estimated daily water consumption (L/day)	Blood lead level (μg/dL)	$R^2 = 0.25$	BLL = 10 + 7 × WLL × water consumption (units adjusted)	Savard, 1992
School children in southern Saxonia, Germany ($n = 69$ for location A, $n = 44$ for location B)	Composite tap water lead (μg/L)	Blood lead level (μg/dL)	Location A: $R^2 = 0.34$ Location B: $R^2 = 0.41$	Location A: Log(BLL) = 0.74 + 0.14Log(WLL) Location B: Log(BLL) = 0.81 + 0.14Log(WLL)	Englert et al., 1994
Mothers in Glasgow, Scotland ($n = 342$)	Water lead (μg/L)	Blood lead level (μg/dL)	Spearman's $\rho = 0.39$	Not determined	Watt et al., 1996
Women in Hamburg, Germany ($n = 142$ for subsample with detectable water lead)	Average water lead (μg/L) from 3 specimens	Blood lead level (μg/dL)	Spearman's $\rho = 0.43$	Not determined	Fertmann et al., 2004
Children in Washington, DC ($n = 2698$ in high risk; $n = 4791$ in moderate risk; $n = 2621$ in low risk)	90th percentile water lead (μg/L)	% Increase in children with EBLL compared with U.S. average	$R^2 = 0.83$ in high risk; $R^2 = 0.71$ in moderate risk; $R^2 = 0.50$ in low Risk	Not determined	Edwards et al., 2009

Note. ALL = air lead level; BLL = blood lead level; DLL = dust lead level; WLL = water lead level.

a very significant concern for this population group. Infants typically consume 500–1000 mL of formula per day (World Health Organization, 2000). If the water used to reconstitute formula contains 90 μg/L of lead, an infant receiving 750 mL of such formula daily would ingest 61 μg Pb/day, based on the illustrative calculation:

$$\frac{90\,\mu\text{g Pb}}{\text{L water}} \cdot \frac{0.75\,\text{L formula}}{\text{day}} \cdot 90\%\,\text{water in formula} = 61\,\mu\text{g Pb/day} \qquad (1)$$

Ryu et al. (1983) found that when infant formula commonly had elevated lead derived from solder, infants consuming daily formula with 61 μg Pb from 3.7–6.5 months of age had elevated blood lead levels by 5.6 months of age (Figure 5). Another group of infants, exposed to only 16 μg Pb/day through their diet, did not develop elevated blood lead (Figure 5). On this basis Ryu et al. (1983) concluded that a lead intake of 16 μg/day, or else 3–4 μg/kg/day, is not associated with elevations in blood lead level above 10 μg/dL. This roughly corresponds to the provisional tolerable weekly intake of 25 μg/kg/week (or else 3.5 μg/kg/day) set by the World Health Organization (2000). The Ryu et al. (1983) study is unique, because it provides unambiguous results for infants whose dietary lead intake was completely controlled. Due to obvious modern ethical concerns, similar experimental studies with infants are unlikely to be repeated.

Later studies also derived strong associations between Glasgow infants' dietary lead (mainly consisting of drinking water) and blood lead (Lacey et al., 1985). For 13-week-old infants, a duplicate of their formula was collected for a week so that their total lead intake could be unambiguously

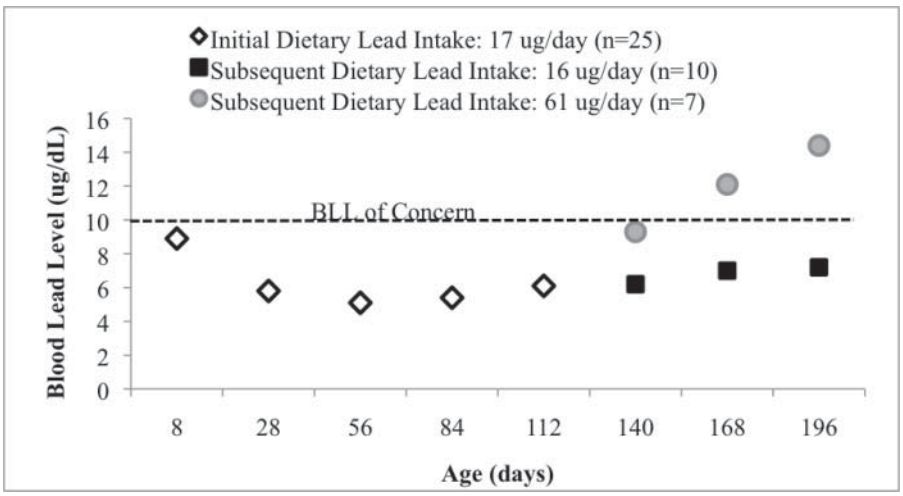

FIGURE 5. Average blood lead level (BLL) versus age for two groups of formula-fed infants, at two levels of dietary lead intake. Adapted from data in Ryu et al. (1983).

quantified. A simple linear relationship between lead in water collected from kettles and infant blood lead level was derived, with a correlation coefficient (R^2) of 0.32 (Table 10). This work demonstrates that due to genetic and other factors mentioned previously, perfect correlations are not to be expected between lead in water and lead in blood, even for the most susceptible subpopulation to lead exposure from water.

An investigation by Shannon and Graef (1992) revealed nine cases where lead poisoning occurred in Boston infants after consuming instant formula reconstituted with lead-contaminated water. In one such case, the formula was prepared each morning with first-draw water from the kitchen tap, which contained 130 μg/L lead attributable to lead solder (Shannon and Graef, 1989). Other cases of elevated blood lead from consumption of formula, with no other source of lead in the child's environment, have been reported (Cosgrove et al., 1989; Lockitch et al., 1991).

Association Between WLL and BLL in Young Children and Adults before Implementation of Modern Corrosion Control

The first survey to show a curvilinear relationship between water lead and blood lead was that of Moore et al. (1977), which yielded a correlation coefficient (R) of 0.52 by analyzing data from different sectors of the Scottish population (Table 10). That work concluded that perhaps the most important aspect of this problem is the effect that high water lead has on the chances of a person having an unduly raised blood lead level. In that study, 18% of people with first-flush water lead $\geq$298 μg/L had BLLs $\geq$41 μg/dL, compared with only 0.3% of those with water lead $<$50 μg/L.

Sherlock et al. (1984), who analyzed lead in water and lead in blood of mothers in Ayr, Scotland, reinforced Moore's notion of a curvilinear relationship (Table 10). Initially, lead in water and in blood were measured for 114 mothers during 1980–1981, when the Ayr water supply was very corrosive and lead pipes were predominant. That analysis yielded a correlation coefficient (R^2) of 0.56 between kettle water lead and blood lead level (Table 10). After changes in water treatment were implemented by increasing the pH from 5.0 to 8.5, and after some of the lead pipes had been removed, the same analysis was repeated during 1982–1983. The sample of women in the subsequent analysis included many of the same women as the 1980–1981 analysis (Sherlock et al., 1984). Combination of both data sets yielded a correlation coefficient (R^2) of 0.65 between kettle water lead and blood lead (Table 10). After increasing the pH of the water supply, water lead levels significantly dropped, and median blood lead levels also dropped from 21 to 13 μg/dL.

A study of 321 adults in an area of France with relatively corrosive water and high incidence of lead pipe (Bonnefoy et al., 1985) revealed that the concentration of lead in tap water was significantly correlated to the residents' BLL (Table 10). For water lead levels up to 20 μg/L, the BLLs of men and

women remained relatively constant, but if lead in water exceeded 20 μg/L BLLs increased substantially. Elwood et al. (1984) assessed the relative contributions of water lead, dust lead, and air lead to blood lead of 192 women in various areas of Wales. The regression model indicated that even in areas with relatively low water lead levels for that time period, water was an important source of blood lead. An increase of lead in water from 0 to 60 μg/L resulted in an increase of 5.5 μg/dL in blood lead level (Elwood et al., 1984).

Raab et al. (1987) assessed the relative contributions of water lead and dust lead to blood lead of 6–9-year-old children in a part of Edinburgh, Scotland, with a high incidence of lead pipes and corrosive water supply. Their resulting model, accounting for exposure to water and dust, explained 43% of the variation in blood lead levels (Table 10). Coefficients for water and dust were significant in their model (Table 10), and the authors concluded that water lead was more important than dust in this population. An 8-year follow-up study of the same individuals in central Edinburgh, showed a dramatic decrease in their water lead and blood lead levels, which was attributed to improved corrosion control and removal of lead pipes from plumbing (Macintyre et al., 1998).

Maes et al. (1991) assessed the contribution of lead from drinking water, dust, soil, and paint to BLLs of 384 individuals of various ages in Hawaii. This study relied on measurements from exterior house faucets previously conducted on behalf of the Department of Health. Lead in paint, dust, and soil was measured, and information on water consumption patterns and demographics was obtained through questionnaire responses of the participants. Because this population was exposed to relatively high levels of lead from water and low levels of lead from soil, dust, and paint, the authors found a stronger rank-based correlation of BLLs with WLLs ($r = 0.53$), compared with other environmental sources ($r = 0.35$ for soil, 0.30 for dust, and 0.14 for interior paint; Maes et al., 1991). Blood samples in this study were collected more than 2 months after residents had been informed to avoid tap water, unless it tested below 20 μg/L, and virtually no vulnerable young children (<1 year of age) were tested. Even though the work of Maes et al. (1991) was never published, it was submitted to the US EPA to influence formulation of the 1991 US EPA LCR, which in turn introduced modern corrosion control strategies for lead in U.S. drinking water.

Association Between WLL and BLL in Young Children and Adults After Implementation of Modern Corrosion Control

More recent studies, conducted after the phase-out of lead in gasoline and other lead reduction strategies, and with much lower water lead levels due to modern corrosion control, still indicate strong relationships between lead in blood and lead in water. An epidemiological study in Hamburg, Germany (Fertmann et al., 2004), found a statistically significant correlation between

average lead concentration in tap water and lead concentration in blood for 142 young women (Spearman's $\rho = 0.43$, $p < .0001$; Table 10). For those women who were exposed to water lead >10 μg/L, an intervention program was tested, which either involved eliminating tap water lead exposure (by consuming bottled water) or minimizing exposure (by flushing water prior to consumption). Overall, after about 10 weeks of intervention, the median blood lead level decreased by 1.1 μg/dL ($p \leq .001$). Individuals flushing the water lowered their blood level by 21%, whereas those drinking bottled water reduced their blood lead level by 37% (Fertmann et al., 2004). Fertmann et al. (2004) concluded that lead in tap water stands for an avoidable surplus exposure.

In another German study conducted in southern Saxonia, lead in blood and lead in tap water were measured for school children from two locations, A and B, respectively (Englert and Horing, 1994). Lead pipes were used in about 50% of their houses. After log-transformation of their blood lead levels and their drinking water lead levels, 34% of the variation in blood lead levels was explained by log-WLL in location A (i.e., $R^2 = 0.34$ for location A), and 41% of the variation was explained in location B (i.e., $R^2 = 0.41$ for location B; Table 10). These authors concluded that in this part of Germany, lead exposure through drinking water was a greater concern than lead paint and other sources, due to the lead pipes in the water supply that had not yet been removed. Seven years later, after many lead pipes had been replaced with alternative materials, another study quantified WLLs in homes of newborn babies in various regions of southern Saxonia (Zietz et al., 2001). Overall, 3.1% of the 1,434 stagnation samples had lead higher than 10 μg/L. But certain geographic regions were at higher risk (>5% above 10 μg/L), and these authors concluded that the exceptional cases were due to leaching of domestic plumbing and fittings containing lead (Zietz et al., 2001).

Following a case of lead intoxication by drinking water in Sainte-Agathe-des-Monts, Canada, a study demonstrated a link between EBLLs and WLLs, as well as presence of lead service lines (Savard, 1992). Canada did not provide guidance for national corrosion control programs until 2009 (Health Canada, 2009) and this town still distributed corrosive water. On the basis of field investigations and 383 blood lead analyses, BLLs higher than 20 μg/dL were associated with the presence of lead service lines, Yates's $\chi^2() = 5.85, p = .02$ (Savard, 1992). A mathematical model was developed for the 72 citizens for which WLLs were measured (Table 10). Lead concentrations in those samples were as high as 4200 μg/L. Water consumption was obtained on the basis of a questionnaire. Using a linear regression between BLL and the estimated lead daily intake, a correlation coefficient (R^2) of 0.25 was obtained (Savard, 1992). The water corrosivity was rapidly identified as the problem (pH as low as 4.8 measured in some houses) and corrective measures were taken by increasing the pH to 8.4. After less than a month, WLLs were reduced by more than 90%, and the measured BLLs were significantly reduced by

24% in less than a year. Work with lead paint or dust mitigation has also demonstrated that, in some cases, mitigation of the suspected lead hazard only slightly reduces blood lead, if high levels of lead have been stored in bone (Gwiazda et al., 2005; Rust et al., 1999).

Watt et al. (1996) assessed the relationship between tap water lead and maternal blood lead concentrations in Glasgow, Scotland, after the water supply was subjected to maximal water treatment to reduce plumbosolvency. Tap water lead remained the main correlate of raised maternal blood lead concentrations, accounting for 76% of cases of maternal blood lead concentrations above 10 μg/dL. The authors concluded that although tap water lead and maternal blood lead concentrations had fallen substantially since the early 1980s, tap water lead was still a public health problem in that area, especially for the estimated 13% of infants who were exposed via bottle feeds to tap water lead concentrations exceeding the World Health Organization guideline of 10 μg/L.

Lanphear et al. (2002) assessed the contribution of lead in water versus other sources to children's blood lead levels during early childhood. Children from 6 to 24 months old were monitored in Rochester, New York, a community not considered to have lead-in-water problems according to the US EPA LCR. Samples of tap water, house dust, soil, and paint were quantified for lead, with house dust being determined as the main source of lead exposure. Even so, water lead concentration was also directly associated with blood lead levels ($p < .001$). Children who lived in housing with water lead concentration greater than 5 μg/L had slightly higher (1.0 μg/dL) blood lead levels than children who had home water lead levels below 5 μg/L (Lanphear et al., 2002).

Taking into account geographic risk factors during an incident of suboptimal corrosion control, Edwards et al. (2009) found a strong correlation between the frequency of EBL and the 90th percentile lead in water concentration from 2000–2007 in Washington, DC. In neighborhoods determined to have the greatest frequency of lead pipe and highest lead concentrations, a correlation was found for children less than 30 months of age (Table 10). Older children, children living in neighborhoods with relatively few lead pipes or measurements of elevated lead in water showed lesser impacts. But the youngest children (<1.3 years) showed very strong correlations between the incidence of EBL and the reported 90th percentile lead in water concentration. Earlier studies on Washington, DC (Guidotti et al., 2007; Stokes et al., 2004), did not focus on the youngest children or geographical factors, and saw little or no increased incidence of EBL during the time of high lead in water.

Studies That Did Not Find an Association Between WLLs and BLLs

Many other studies have found little or no relationship between lead in blood and lead in water. These studies are occasionally cited as if results

are contradictory to those highlighted in the preceding section. That work is critically reviewed herein, in an attempt to reconcile results that are superficially in conflict, but which are consistent with biokinetic understanding of relationships between lead in water exposure and lead in blood.

Lack of Association Between WLL and BLL When Lead in Water Was Reportedly Low

There are many areas in the United States (and other countries) in which water lead concentrations are very low. This can occur in situations with modern plumbing which has no lead pipe, lead solder, or leaded brass, and with optimized corrosion control that can dramatically reduce lead leaching. Some older cities with high incidence of lead pipe and lead solder have pipes that are virtually completely lined by scale such as calcium carbonate, which effectively eliminates contact between the lead-bearing plumbing and the water. In such circumstances lead in water will not be a dominant, or even a significant contributor, to overall lead exposure.

For instance, in a study by Lubin et al. (1984) where water samples were collected in the homes of 50 children with BLL >30 μg/dL in Columbus, Ohio, lead in water was always low (<10 μg/L). It is believed that the water supply in that study was atypically noncorrosive (high pH of 9.6 and high hardness of 101 mg/L). Not surprisingly, there was no correlation between lead in water and lead in blood, even in the presence of lead pipes at the children's homes. Likewise, a study in Germany (Meyer et al., 1998) in a town where lead in tap water was extremely low (<1 μg/L) found no significant association between lead in domestic water and in blood for children. Another study of children's BLL in Miami, Florida (Gasana et al., 2006), also found no association of BLLs to WLLs (Spearman's $\rho = 0.03$ for flushed water samples and 0.005 for first-draw water samples). Water lead measured in 120 homes was reportedly low (<15 μg/L), with the exception of three homes. However, correlations between BLL and floor dust ($\rho = 0.27$) and windowsill ($\rho = 0.28$) were statistically significant ($p < .05$; Gasana et al., 2006).

Another important study by Rabinowitz et al. (1985) examined the association of BLLs of infants in Boston with lead in dust, soil, indoor air, paint, and tap water. The authors found statistically significant correlations of children's BLL at age 24 months with lead in dust (Spearman's $\rho = 0.4$, $p < .0001$), with lead in soil (Spearman's $\rho = 0.3$, $p < .001$), and with lead in paint (Spearman's $\rho = 0.2$, $p < .01$), but not with lead in water (Spearman's $\rho = 0.14$, $p =$ ns). The conclusions of that work regarding important contributions of dust, soil, and paint to BLL are consistent with expectations. However, analytical limitations in quantification may have masked any potential contribution of WLL to BLL, if it were present. Specifically, lead in water was quantified using anodic stripping voltammetry. This analytical technique has recently been shown to accurately measure dissolved Pb^{+2},

but to not measure particulate lead or Pb^{+4} levels in water (Cartier et al., 2009). The latter species have recently proved to be present in drinking water under at least some circumstances (Triantafyllidou et al., 2007), but were not understood at the time of the Rabinowitz et al. (1985) study. Moreover, samples were allowed to sit unacidified before analysis, which is now recognized to potentially miss some of the lead present in water (M. Rabinowitz, personal communication, December 10, 2006). Perhaps, partly because of these issues, only very low levels of lead (3.7–7.3 μg/L) were reported for Boston drinking water samples (Rabinowitz et al., 1985).

To provide a historical perspective for Boston, Potula et al. (1999) found lead in water of Boston homes as high as 169 μg/L during the same time period. Boston water, which was linked to lead poisoning via infant formula, was reported by Shannon and Graef (1989) to contain 132 μg/L. Even as late as 1996–2000, lead levels in first-draw tap water samples from Boston were 159 μg/L on average, and as high as 311 μg/L in the worst case for children with elevated blood lead (State of Massachusetts, Water Quality Assurance Section, Drinking Water Program, personal communication, November 2006). Even flushed water samples for lead poisoned children in the 2009 data from Massachusetts contained as high as 146 μg/L lead.

Lack of Association Between WLL and BLL When Lead in Water was Reportedly High

Some studies have found no association between elevated lead in water and elevated lead in blood. Key aspects of such studies are critically reviewed herein, especially as they relate to potential limitations described in preceding sections (see Table 10). For example, Costa et al. (1997) reported that very high water lead levels in a public school in rural Utah (up to 840 μg/L) did not cause EBLL. In that study, measurements of blood lead were undertaken for only 40% of students, more than 16 days after notification of the problem and advice to drink bottled water, during which time lead in blood could drop, considering its half life of around one month (World Health Organization, 2000). Even though one case of elevated blood lead was identified, it was dismissed as unrelated to water lead (Costa et al., 1997).

A CDC study reported that in 201 cases where home tap water contained more than 300 μg/L of lead in Washington, DC, none of the individuals were found to suffer from EBLL (Stokes et al., 2004). Another study on the same topic cited the same data, and did not find an association between elevated lead in water and lead in blood, concluding that there appeared to have been no identifiable public health impact from the elevation of lead in drinking water in Washington, DC, in 2003 and 2004 (Guidotti et al., 2007). Neither study focused on infants, who are most vulnerable to harm from lead in water. In addition, both studies lumped all the blood lead data for Washington, DC, together, an approach that masked disparities among different neighborhoods (Edwards et al., 2009). Finally, as mentioned previously, virtually

no residents had been consuming tap water for months prior to having their blood lead drawn, rendering the data useless for assessing impacts of lead in water on lead in blood (CDC, 2010b; Edwards et. al., 2009). The no-harm conclusion of Guidotti et al. (2007) has since been removed (Guidotti et al., 2009).

Studies That Did Not Measure Lead in Water at Homes

Some researchers attempted to assess the contribution of lead in water to lead in blood, without measuring lead in tap water at homes. For example, studies occasionally relied on qualitative data obtained from questionnaires regarding consumers' water consumption habits (tap water vs. filtered or bottled water) or knowledge regarding the presence of lead pipes in consumers' home plumbing. Other studies relied on lead-in-water measurements obtained from the distribution system and not home taps, which can result in overlooking tap water as a potentially important source.

For example, a broad Cincinnati study aimed to investigate different lead sources and factors which result in excessive intake for children in urban settings (Bornschein et al., 1985; Clark et al., 1985). Blood lead levels were systematically monitored from birth through 5 years of age and a broad range of lead sources in the children's environment were accounted for, including painted surfaces and dust, soil samples in outside playing area, street dirt, and any suspicious items that the children were mouthing. Water samples were not collected in this otherwise very thorough and definitive study. Instead, sampling data collected by the water utility from the distribution system, before the water even enters the service line where lead hazards are introduced (see Figure 1), were cited as having lead concentrations <6 μg/L (Clark et al., 1985). Exposure from water was thus deemed to be insignificant when, in fact, samples were never collected in a manner that would allow risks to be quantified if they were present. Historical data from Greater Cincinnati Water Works suggest that even in recent years, with modern corrosion control, some Cincinnati schools had tap water lead levels above 15 μg/L, while some homes tested at 180 μg/L after partial lead pipe replacements (DeMarco, 2004).

A study in Northern France (Leroyer et al., 2000) showed that BLLs doubled for children who reported consuming tap water in homes with lead plumbing identified under the kitchen sink. In cases where lead pipes were not visible under the kitchen sink, children drinking tap water still had significantly higher BLLs compared with those consuming bottled water (Leroyer et al., 2000). Leroyer et al. (2000) qualified their conclusions by suggesting that water sampling should be conducted to more carefully assess their findings, which relied on visual identification of lead plumbing and qualitative answers to a questionnaire.

Synthesis of Studies on the Association Between Lead in Water and in Blood

Rigorous scientific studies prior to implementation of modern corrosion control provided strong links between elevated lead in water and elevated blood lead (i.e., >10 μg/dL) of exposed populations. As would be expected based on present understanding of dietary intake and hand-to-mouth behavior relative to significance of lead sources, impacts of elevated lead in water on lead in blood become more significant the younger the child, with especially high risks for children consuming reconstituted infant formula. The work of Lacey et al. (1985) and Ryu et al. (1983) exemplifies rigorously controlled studies that are unlikely to be improved on in the near future, and which served as the basis for the US EPA LCR and models predicting BLL developed by the US EPA.

Two landmark multimedia U.S. studies (Bornschein et al., 1985; Rabinowitz et al., 1985), did not find any association between lead in water and in blood for children in Cincinnati and Boston, respectively. The strong relationships established in that research between lead in paint, dust, and soil and children's blood are not disputed, but each study had limitations or gaps in quantifying lead in water risks.

More recent studies in Canada, Germany, the United Kingdom, and the United States sometimes found strong associations between WLLs and BLLs, and sometimes not. These studies reflect marked differences in the extent of lead-in-water exposure based on plumbing materials, corrosivity of the water, and other nuances of exposure. Some recent work by the CDC and others that concluded very high lead in water (> 300 μg/L) did not impact incidence of EBL in an exposed population has been reanalyzed, corrected, or clarified (CDC, 2010b; Edwards et al., 2009; Edwards, 2010; Guidotti et al., 2009; Miller, 2010). That work is no longer inconsistent with decades of prior research. Other work has demonstrated strong links between lead in water and lead in blood even at much lower levels of lead in water exposure, in systems conducting optimized corrosion control or its equivalent (Englert et al., 1994; Fertmann et al., 2004; Lanphear et al., 2002).

VIII. SUMMARY AND CONCLUSIONS

As efforts shift from addressing pervasive lead sources that elevate the blood lead of large percentages of the population, to more isolated individual cases requiring exceptional attention, it will be necessary to more carefully consider lead in water as a potential source.

Although routine blood lead monitoring and environmental assessments are not designed to detect lead in water hazards when present, several recent cases of elevated blood lead in the United States and other countries have

been attributed to lead-contaminated drinking water. Existing U.S. regulations and guidelines have not eliminated lead in water hazards in systems served by public water supplies, schools, day cares, and privately owned homes.

Lead in drinking water originates from lead-bearing plumbing materials, which undergo corrosion reactions, and may severely contaminate the water supply. Contrary to popular belief that lead-in-water problems invariably decrease as water systems age and rust/scale develops on pipes, problems with sporadic detachment of rust/scale on lead-bearing plumbing might create acute human health risks that are hard to detect and link to elevations of lead in blood. Up to 81 million U.S. homes are estimated to be at potential risk due to the presence of lead pipe and lead solder, and even new homes can occasionally experience high lead from brass/bronze plumbing. The occurrence of particulate lead in U.S. drinking water has not been adequately examined, but case studies suggest that the highest doses of lead are associated with the presence of particulate (and not dissolved) lead in tap water.

When water lead measurements are not available at high-risk taps, or when they fail to quantify the actual lead content of drinking water, correlations of water lead with health risks may be missed. A strong association between lead in water and lead in blood has been documented through decades of prior scientific research. Epidemiological studies in the United States, the United Kingdom, Germany, France, and Canada indicate that elevated lead in water can occasionally be the dominant, or a major contributor, to elevated blood lead. Re-evaluation of the public health risk from lead in water, with emphasis on particulate lead and sensitive subpopulations, is timely considering forthcoming revisions to the LCR and acknowledged deficiencies in addressing lead in school drinking water.

IX. RESEARCH NEEDS

This literature review highlighted the need for additional research on lead occurrence in tap water and associated public health risks. Specifically, the occurrence of lead in drinking water at U.S. schools needs to be systematically monitored, using sampling protocols that will allow identification of the source(s) of potential problems and development of concise remedial actions. Detailed case studies on lead-in-water at schools could then be synthesized, and serve as a guide for schools that encounter similar problems in the future.

The effects of sampling protocol (e.g., flow rate, cold vs. hot water) and sample handling (e.g., sample preservation and holding time) on lead detection need to be evaluated for all situations including schools, homes, and other buildings. Subtle differences in sample collection procedures can

either detect or completely miss lead spikes, especially when problems with particulate lead in water are important. The occurrence of particulate lead spikes in U.S. drinking water needs to be better characterized because it may result in intermittent exposures of acute health concern, which can easily go undetected. Acute health effects from lead in water, concentration of lead in food, and potential exposure to elevated lead from hot water deserve explicit consideration.

Old lead service lines are a major contributor to lead levels at the tap, when they are present. Partial replacements of lead service lines in response to provisions of the LCR, as a means of reducing lead-in-water exposure, require re-evaluation in light of preliminary data showing short- and long-term problems with lead spikes and increased risks of elevated blood lead in children. Laboratory studies quantifying the long-term impacts in a range of waters, as well as the cost and benefit of the procedure, are necessary. Likewise, evaluation of impacts from newly installed leaded brass plumbing devices is also needed.

Past approaches in modeling health impacts from elevated lead in water, based on prediction of the geometric mean BLL, were useful when considering impacts on populations. But as society shifts its concern to tracking and addressing individual cases of childhood lead poisoning, modeling approaches need to consider and predict impacts on susceptible individuals exposed to the highest sampled lead in water concentrations.

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